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PURPOSES

The main purpose of the Physiological Reviews is to furnish a means whereby those interested in the physiological sciences may keep in touch with contemporary research. The literature, as every worker knows, is so extensive and scattered that even the specialist may fail to maintain contact with the advance along different lines of his subject. The obvious method of meeting such a situation is to provide articles from time to time in which the more recent literature is compared and summarized. The abstract journals render valuable assistance by condensing and classifying the literature of individual papers, but their function does not extend to a comparative analysis of results and methods. Publications such as the Ergebnisse der Physiologie, the Harvey Lectures, etc., that attempt this latter task, have been so helpful as to encourage the belief that a further enlargement of such agencies will be welcomed by all workers. It is proposed, therefore, to establish a journal in which there will be published a series of short but comprehensive articles dealing with the recent literature in Physiology, using this term in a broad sense to include Bio-chemistry, Bio-physics, Experimental Pharmacology and Experimental Pathology.

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THE AMERICAN
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VOL. 58 DECEMBER 1, 1921 No. 2

STUDIES IN NUTRITION[1]

THE CHOICE BETWEEN ADEQUATE AND INADEQUATE DIET, AS MADE BY RATS AND MICE

HELEN S. MITCHELL AND LAFAYETTE B. MENDEL

From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven, Connecticut

Received for publication July 7, 1921

The choice of food is presumably guided by what is commonly called appetite. The causes of appetite and hunger in the young animal as well as the psychological aspects of the subject have been discussed by Goodall (1) and Carlson (2). According to Carlson it would seem that a limited exercise of choice is evidenced even in the very young. Whether it be instinct or appetite or some other propensity which guides an individual in the selection of his food, the fact remains that in his natural environment the wild animal does choose a diet which is adequate for his needs. It is admitted that his choice is reliable under such circumstances; but the question arises: "Can instinct guide the animal advantageously when there is a limited variety of food available?"

The experimental work of Evvard (3) and Osborne and Mendel (4) indicates that under the conditions prescribed the "self-fed" animals did as well if not better than those on definite rations. Sherman (5) and Chittenden (6) also believe that appetite is at least partially reliable as a guide to nutrition. Crichton-Browne (7) expresses unqualified faith in the dietary habits and hereditary customs of mankind, while Hutchinson (8) believes that the appetite of the growing child is far more reliable than the nutritional standards of either mother or physician. Jordan (9),

[1] The data in this paper are taken from the dissertation presented by Helen S. Mitchell for the degree of Doctor of Philosophy, Yale University, 1921.

on the other hand, in speaking of cattle feeding says that a nutrition expert is better qualified to select the ration "than any cow ever grown."

That food prejudices arising from habit or custom are frequently poor guides to nutrition in immigrants is evidenced by the malnutrition among certain nationalities where the diet is not adapted to the new conditions of life in America (10). Stefansson (11) noted that appetite of his dogs was influenced by habit or prejudice with a consequent refusal to eat new foods offered.

The foregoing conflicting views concerning the reliability of appetite as a guide in nutrition leave the subject open for further discussion. Since swine had been used most extensively in previous experimental work, it seemed that a similar investigation with other species might furnish a valuable contribution to the subject. One series of experiments was therefore conducted with the idea of reinvestigating and extending, with a larger variety of choices, the experiments reported by Osborne and Mendel (4) in 1918. The question to be considered was whether rats and mice would choose or proportion their diets so as to promote normal growth when given a choice between two "*synthetic*" *food mixtures* differing only in the type or amount of a single constituent. Observations were also made on the ability of rats to select an adequate diet when a choice of *natural foods* was offered. A third type of investigation was concerned with the food prejudices of rats and mice.

Technic and methods employed. The methods employed in the caging and feeding of rats were those described by Ferry (12). Where two paste foods were offered two cups occupied the holder, making the foods equally accessible. A particularly convenient form of mouse cage used in the work facilitated handling and made possible an accurate determination of food intake (13). Animals were weighed twice a week and foods once a week.

Curves of successive body weight representing the average growth of animals on essentially adequate diets have been used as bases for comparison with curves of growth for animals on "free-choice" diets. The curve of normal growth for the corresponding sex and species is represented on all charts by a broken line. Food intake is plotted as the total amount eaten per week.

To avoid practical difficulties in feeding and to lessen the number of factors involved, most of the experiments have followed the plan of offering only two possibilities of choice to an animal.

Choice of "synthetic" foods. The largest series of experiments has aimed to carry out the previously cited idea proposed by Osborne and Mendel (4) of offering two foods differing only in the type or amount of a

single food principle incorporated in the mixture. An attempt was made to keep the consistency and appearance of the two foods as nearly alike as possible. Yeast was used as the source of vitamin B in all cases except where "protein-free milk" was added to supply this food accessory. The factors involved in these "free-choice" diets were secteled from among those which had proved most problematical and therefore interesting in many attempts which have been made to formulate an adequate and well-balanced diet for rats and mice. The types of choices offered in the form of "synthetic" paste foods were as follows:

1. High and low content of protein.
Rats: Foods containing 18 per cent vs. 4.5 per cent of casein.
Mice: Foods containing 31 per cent vs. 7 per cent of casein.
2. "Complete" and "incomplete" protein.
Rats: Foods containing 18 per cent casein vs. 18 per cent of zein.
Mice: Foods containing 31 per cent casein vs. 31 per cent of zein.
3. High and low content of vitamin A.
Rats: Foods containing 9 per cent of butter fat vs. lard fat.
Mice: Foods containing 10 per cent of butter fat vs. lard fat.
4. High and low content of vitamin B.
Rats: *a*. Foods containing 28 per cent of natural "protein-free milk" vs. artificial "protein-free milk."
b. Foods containing 2 per cent of yeast vs. no yeast.
Mice: *a*. Foods containing 40 per cent of natural "protein-free milk" vs. artificial "protein-free milk."
b. Foods containing 2 per cent of yeast vs. no yeast.
5. High and low content of inorganic salts.
Rats: Foods containing 4 per cent of salt mixture vs. none.
Mice: Foods containing 7 per cent of salt mixture vs. none.

The standard rat food used by Osborne and Mendel(4) which was made the basis for the diets in the present investigation and variously modified as the problem required, had the following composition: casein, 18; starch, 49 to 51; salt mixture,[2] 4; butter fat, 9; lard, 20 to 18 per cent respectively.

The composition of the standard mouse food was based on that of a mixture fed by Thompson (14) and on data found in unpublished investigations of Miura (15): casein, 31; starch, 38–40; salt mixture,[2] 7; butter fat, 10; lard, 14–12 per cent respectively.

Commercial products such as casein, cornstarch and lard were pure enough for the purpose of the present investigation. Butter fat was prepared essentially according to Osborne and Mendel (16).

[2] The salt mixture employed in this investigation was furnished from the Connecticut Agricultural Experiment Station where it had been prepared according to the formula given by Osborne and Mendel (18).

The Connecticut Agricultural Experiment Station kindly furnished the zein (17) and "protein-free" milk (17) used in certain of the rations as well as the dried brewery yeast made into convenient sized tablets for feeding. Since 0.4 gram of this yeast has been found to furnish an adequate daily allowance of vitamin per rat, this amount was offered to each rat except where vitamin B was the variable factor in the diet. In the case of mice experiments previous investigators have incorporated the yeast or other vitamin preparations in the food mixture. In general the practice of supplying vitamin preparations apart from the food has been found advisable in order to insure an adequate and regular intake of them even when the food intake is small.

Since in feeding mice 2 per cent of yeast has been found adequate for vitamin B where the daily food intake averaged $2\frac{1}{2}$ to 3 grams, an allowance of 0.05 gram of yeast per mouse was fed daily apart from the food. Occasional difficulty was experienced with very young mice in inducing them to eat the yeast, but after they had been once enticed to taste it they ate the tablets with greed as soon as they were placed in the cages. "Protein-free milk" or yeast incorporated in the food was used as the source of vitamin B in the experiments where the choice involved the latter factor.

Fresh foods were prepared every 2 or 3 weeks according to the method given by Ferry (12).

Choice of natural foods. Rats only were used in this series of experiments because they are less apt to scatter the dry foods than are the mice, and the larger quantities of food eaten make the errors due to scattering less significant when attempting to make accurate determinations of food intake. Ground whole corn and meat meal and salt mixture, a combination of which in some proportion would seem to afford a growth-promoting ration, were offered to these animals.

Care was taken in grinding the corn to produce a meal so fine that no chance would be given to the rats of selecting any special part of the kernel. The meat was prepared by thoroughly drying lean round-steak and then grinding to a meal. No difficulty was experienced with the rats scattering the meat meal and very little with the corn as long as they were acquiring an adequate ration.

Kjeldahl determinations made on the meat meal and ground corn gave the following results:

Meat meal: 12.64 per cent N = 79 per cent protein (N × 6.25)

Ground corn: 1.52 per cent N = 9.5 per cent protein (N × 6.25)

Results of feeding experiments with choice of synthetic foods. With a view to conserving space in the succeeding pages, only a few typical

records and illustrations have been selected out of a considerably larger number of actual trials.

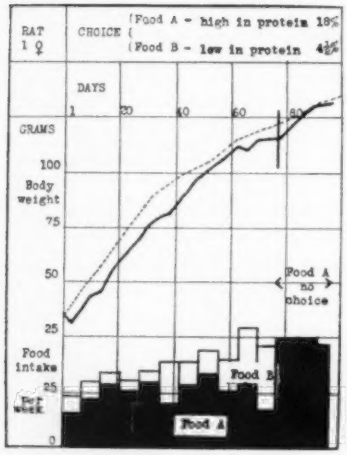

Chart 1

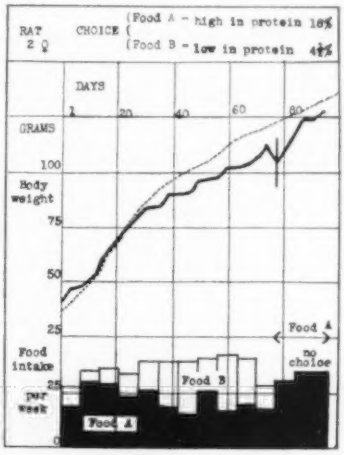

Chart 2

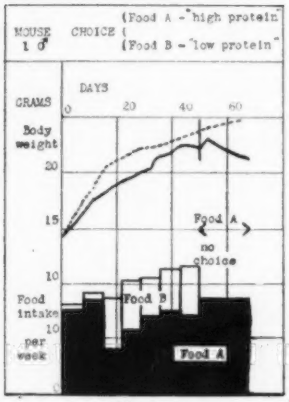

Chart 3

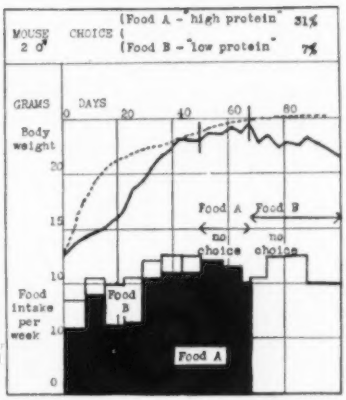

Chart 4

Rats 1♀ and 2♀ (charts 1 and 2) given the choice between foods high and low in protein, selected a diet which enabled them to grow at a practically normal rate. Since 4.5 per cent of casein, the proportion in the inferior mixture, has been demonstrated by Osborne and Mendel (19) to be inadequate for growth and since a control rat in

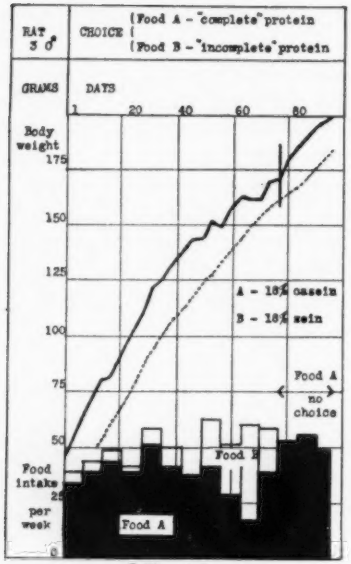

Chart 5

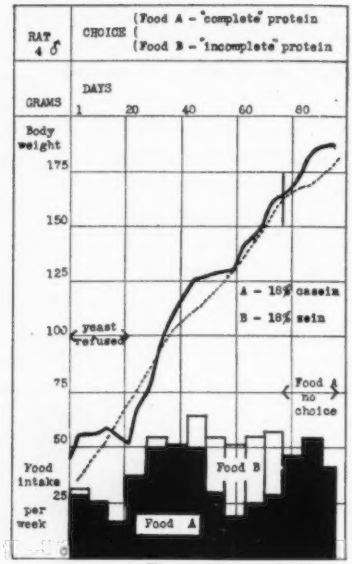

Chart 6

present investigation barely maintained weight on such a diet, it is evident that a food richer in protein is necessary for normal growth.

Mice on a similar choice between foods high and low in protein selected diets which promoted normal growth in young (mice 1♂ and 2♂; charts

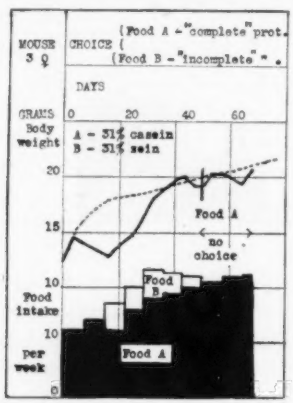

Chart 7

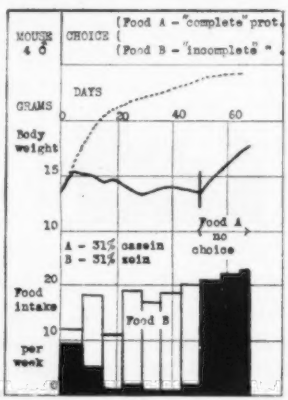

Chart 8

3 and 4) and maintenance in the adult. Animals on the superior mixture alone showed no better rate of growth than on the "free-choice" diet, while mice on the inferior food were distinctly retarded in development. It therefore seems that both rats and mice can select the amount of protein necessary for their physiological needs.

Rats 3♂ and 4♂ (charts 5 and 6) given the choice between two foods containing 18 per cent of casein and 18 per cent of zein respectively, grew at a practically normal rate while eating some of each food offered. Since zein is admitted to be incomplete as the sole source of protein in the diet it is evident that enough casein food was eaten to supply the indispensable amino-acids in which zein is deficient. No change in rate of growth was noted when casein food alone was offered during the last 3 weeks of the experiment.

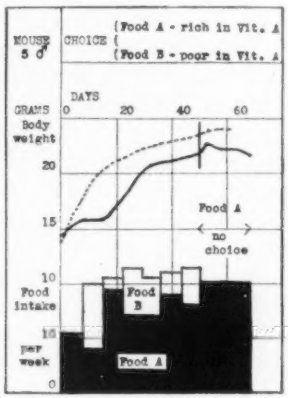

Chart 9

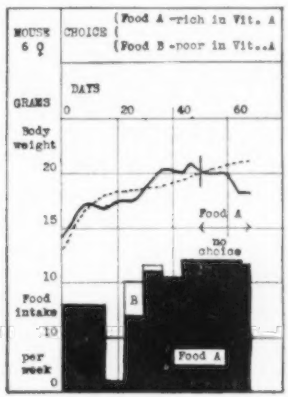

Chart 10

Mice on a similar choice between foods containing different types of protein—casein and zein—did not all choose diets which were advantageous for growth or maintenance. Mouse 3♀ (chart 7) alone succeeded in selecting an adequate diet while mouse 4♂ (chart 8) and an adult mouse showed nutritive decline while choosing largely the zein food but indicated a capacity for normal development when given only the superior mixture. These cases are thus specifically noted because out of many trials these two mice represent the only exceptions to advantageous selections in the choice of diets by either rats or mice.

Experiments in which foods rich and poor in vitamin [1]A were offered to rats were somewhat indecisive because the inferior food was found

to contain enough of that accessory to maintain a rat in fairly good condition throughout a period such as the experiment covered.

A similar choice between foods differing in their content of vitamin A was offered to mice with more satisfactory results. The young mice 5♂ and 6♀ (charts 9 and 10) grew at a practically normal rate while selecting the vitamin-rich food in the larger proportion. The diet chosen by an adult mouse though comparatively lower in vitamin A was nevertheless adequate for maintenance and even for slight growth. The inferior mixture in this case was poor enough in vitamin A to cause nutritive decline in two mice. One recovered after the ingestion of cod liver oil while the other died after several unsuccessful attempts to induce it to take the oil. The potency of liver oils or butter fat in relieving the symptoms of vitamin A deficiency in rats has been well established by Osborne and Mendel (20), (21). Since at the present time there are conflicting views as to the precise rôle of vitamin A in the diet, the significance of a choice involving this factor is also a question. It is evident, however, that the mice chose the food which was sufficiently rich in the accessory substance to prevent any obvious disease or decline in body weight.

The choice between foods rich and poor in vitamin B which was offered to rats 7♂ and 8♂ was complicated by the difference in the consistency of the two foods. The "protein-free milk" used as the source of accessory substance in the presumably superior mixture was somewhat granular and caused diarrhea if eaten in large enough quantity to supply the necessary vitamin. The inferior food lacked vitamin B but was otherwise a satisfactory mixture. Both animals ate some of each food but were unable to maintain a normal rate of growth (charts 11 and 12). At the end of 10 weeks the deficiency of the inferior mixture was supplied in the form of 0.2 gram of yeast daily fed apart from the diet. The proportion of this inferior food eaten began to increase almost immediately while the "protein-free milk" food was chosen in decreasing amounts.

Although, in this experiment, normal growth cannot be taken as a criterion of the ability of rats to choose advantageously, it seems unlikely that mere chance was responsible for the definite and consistent change made in their choice after the supplementary addition of the yeast. The inferior food with yeast addendum made a far more adequate diet than the irritating "protein-free milk" food; and the rats were not slow in searching out this better combination.

Two other rats were offered a similar choice except that the superior mixture contained 2 per cent of yeast instead of "protein-free milk"

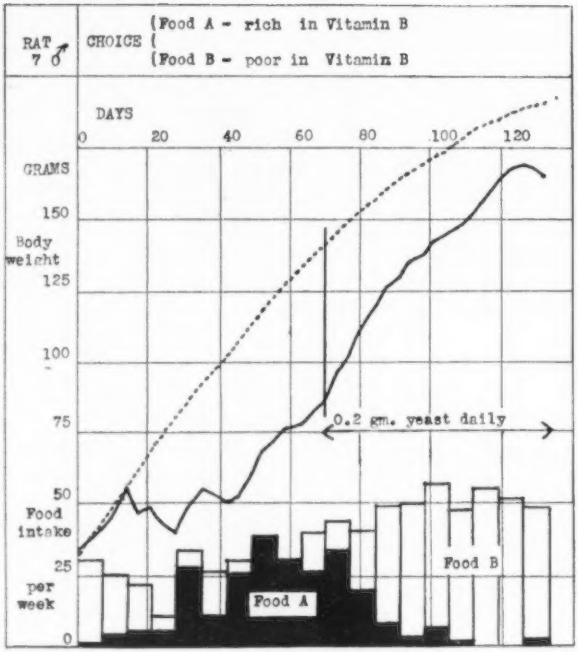

Chart 11

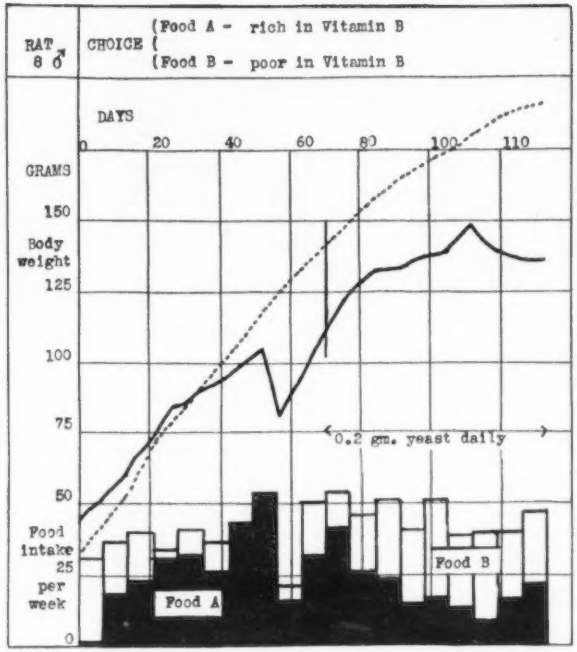

Chart 12

as the source of vitamin B. Growth was normal in both cases although the relative amounts of the two foods eaten varied widely.

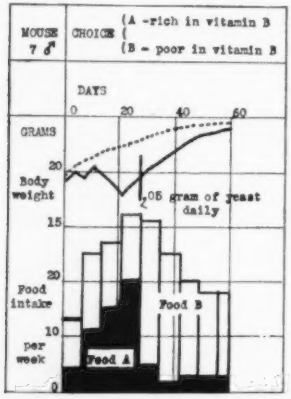

Chart 13

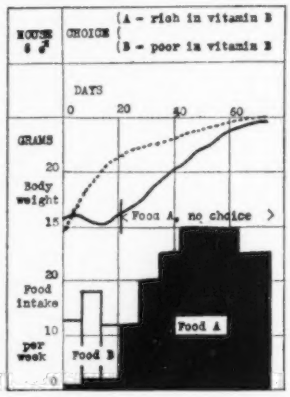

Chart 14

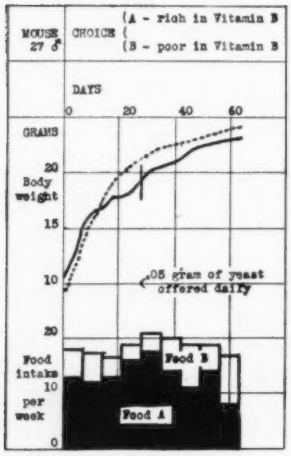

Chart 15

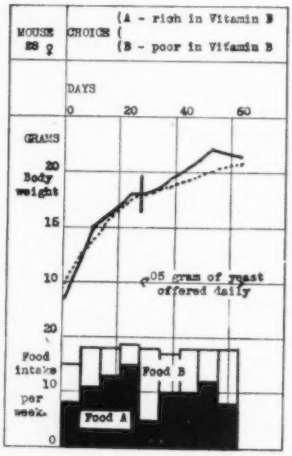

Chart 16

Mice 7♂ and 8♂ (charts 13 and 14) were likewise offered a choice between foods rich and poor in vitamin B. The supposedly superior mixture containing "protein-free milk" caused diarrhea in the mice as the analogous food had done in the rats, thus complicating the factors involved in the choice. Indication of advantageous selection was

given when mouse 7♂, after 4 weeks on the original choice, began eating the inferior food supplemented by 0.05 gram of yeast supplied daily. The growth of mouse 8♂ on the "protein-free milk" food alone shows that this mixture was adequate but probably distasteful and irritating.

The choice offered the mice 27♀ and 28♂ (charts 15 and 16) during the first 4 weeks when the vitamin was supplied by 2 per cent of yeast incorporated in the superior mixture afforded a better index of the ability of these animals to select a diet adequate with respect to vitamin

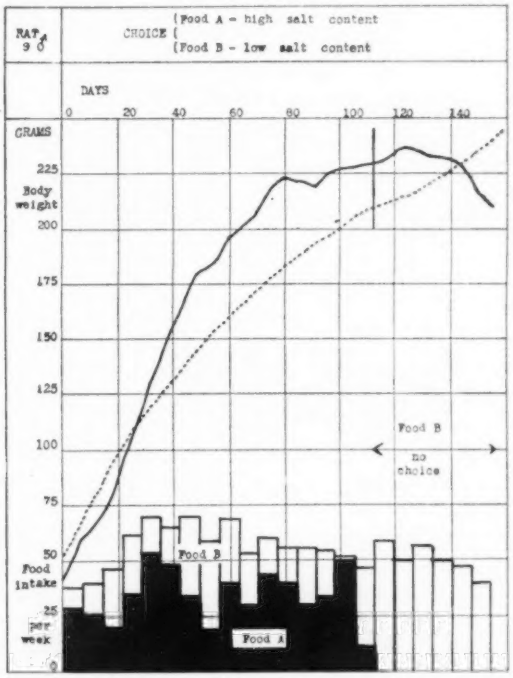

Chart 17

B. The growth of both mice was essentially normal throughout the experiment. The additional 0.05 gram of yeast offered daily during the last 5 weeks caused no marked change in the choice of foods. It may be concluded from the experiments on both rats and mice that a sensitiveness to lack of vitamin B in the diet readily manifests itself so that the animals promptly show a tendency to make good the deficiency, if possible.

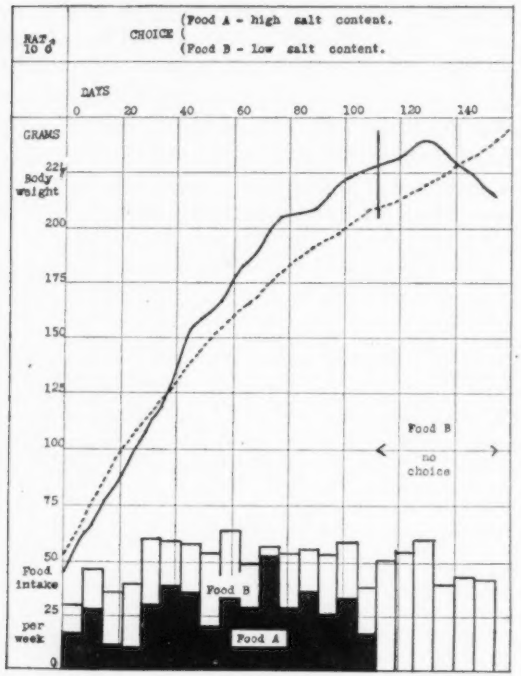

Chart 18

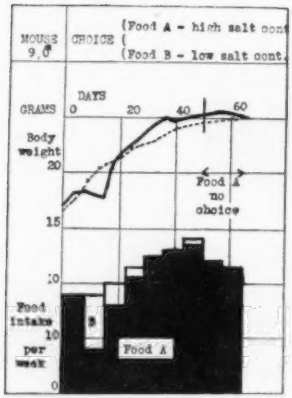

Chart 19

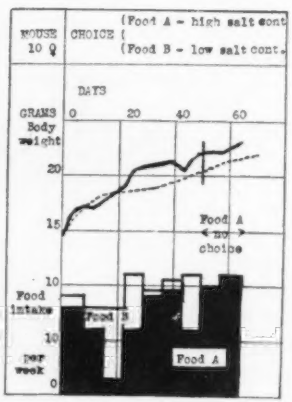

Chart 20

The choice between foods of high and low inorganic salt content was offered to rats 9♂ and 10♂ (charts 17 and 18) and to mice 9♂ and 10♀ (charts 19 and 20). The rats ate a considerable proportion of the "low-salt" food thus bringing the salt content of the total diet down to about 3 per cent. The rate of growth on the "free choice" diet was slightly above the normal. The mice chose the food containing 7 per cent of the salt mixture and maintained a normal or slightly increased rate of growth. Animals of both species fed on the "low-salt" foods all showed retarded development. It may, therefore, be concluded that both rats and mice are capable of choosing diets containing optimum quantities of essential salts for growth.

Choice of natural foods. Ground whole corn, dry meat meal and salt mixture. The natural foods used in this experiment were characterized by their unlike content of protein and carbohydrate, thus affording opportunity for wide variations in the proportion of these two food principles present in a selected diet.

Four rats were offered a choice between ground whole corn and dry meat meal and in addition were allowed free access to the salt mixture such as was used in the "synthetic" food mixtures.

Rats 11♂ and 15♀ which were offered this choice after 8 weeks on paste food showed distinct increment in rate of growth after the change (charts 21 and 22). The question arises whether this stimulation was due to "high protein" or to some unique action of the meat protein. In the case of rats 21♀ and 22♀, which were young animals when the experiment started, the actual proportion of meat eaten was not large, yet was sufficient to supplement the corn ration so as to promote normal growth (charts 23 and 24). In contrast it was noted that a rat fed on *corn alone* grew less well although attempting to acquire the requisite amount of protein by an enormous food intake.

Protein supplied 70 per cent of the calorie yield of the meat meal and 4.5 per cent of that of the whole corn. In the average diet selected by rats 11♂ and 15♀ during the 8 week period on this choice, protein represented 20 and 25 per cent respectively of the total calorie value of the food. In the diet chosen by the younger rats 21♀ and 22♀ protein constituted 12 and 19 per cent respectively. Contrary to what might have been expected the younger animals selected a smaller proportion of protein in their diets than did the older ones. On the other hand none of the rats chose an excessively "high protein" diet although an abundance of the meat meal was always available.

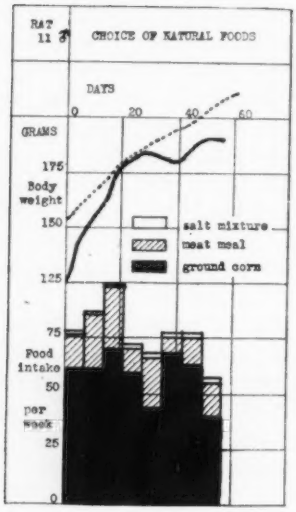

Chart 21

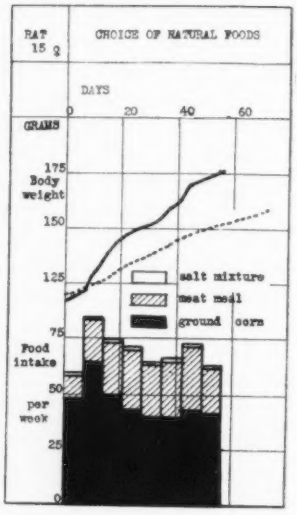

Chart 22

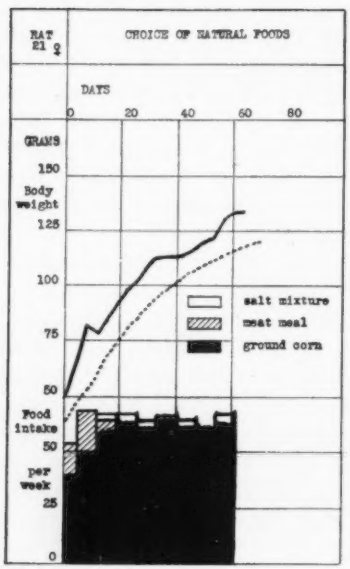

Chart 23

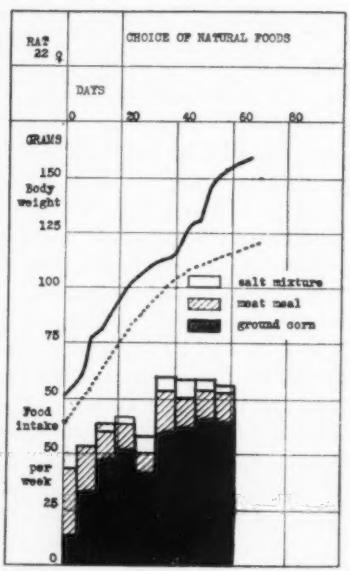

Chart 24

The outcome of this investigation shows in general that in their choices of foods, even between "synthetic" mixtures which appear to the senses to be essentially alike, rats and mice make selections which are as a rule advantageous for their nutritive condition. The choices made tended to promote normal growth in the young and maintenance in the adult even though the proportions of the foods eaten varied with the individual. The results are in harmony with the conclusion earlier expressed by Osborne and Mendel that "the desire of a young animal for food is something more than the mere satisfaction of calorific needs. The demand made by the growth impulse must be met by a food of the proper chemical constitution."

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THE VENOUS SUPPLY OF THE HEART

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1. *The influence of occluding parts of the pulmonary circuit.* The experiments of de Jager (1), Klemensiewicz (2) and Knoll (3) have shown that the respiratory changes in the volume of the lungs exert a profound influence upon the arterial and venous pressures. Contrary to these results, it is claimed by Lichtheim (4) that at least three-fourths of the blood bed of the pulmonary artery may be occluded before an appreciable fall in the carotid pressure is obtained. Plumier (5) arrives at practically the same conclusion. In explanation of these results, R. Tigerstedt (6) calls attention to the fact that the effects of the compression of this vessel may be compensated for by a general vasoconstriction, provided a sufficient time is allowed in which to accomplish this change. Lichtheim's records, however, do not reveal any variations which could possibly be interpreted in this sense. It is stated further by this investigator that the venous pressure suffers no change in consequence of the occlusion of three-fourths of the cross-section of the pulmonary vessels. Accordingly, he draws the conclusion that this adjustment of the pressures is occasioned by an increased flow through those branches of the pulmonary artery which have been left open. Naturally, this augmentation of the flow must be accompanied by a local increase in the pressure. Because of this change, the left side of the heart continues to receive normal quantities of blood which it then delivers to the aorta.

On reëxamination of this subject-matter Landgraf (7) obtained a distinct fall in the carotid pressure on compression of one pulmonary artery. These experiments were performed upon rabbits, the chest having been opened in the median line so as to avoid the collapse of the lungs. Owing to the many technical difficulties connected with this procedure, only four experiments could be completed successfully. In explaining his results, Landgraf lays stress upon the fact that Lichtheim employed curarized animals and instituted artificial respiration. This explanation, however, cannot be regarded as correct, because Licht-

heim also reports one experiment upon a non-curarized rabbit, in which only one lung was collapsed while the other was expanded normally. On compression of the pulmonary artery on the side of the collapsed lung no change in the carotid pressure could be noted.

Very similar experiments have been performed by R. Tigerstedt (8). After the establishment of a unilateral pneumothorax, the lung of this side was ligated at its hilum. If the opposite lung now fulfilled its function properly, the carotid pressure remained the same, whether the lung was merely collapsed or was ligated. Thus, Tigerstedt confirms the work of Lichtheim, but expresses the belief that the blood supply of the different lobes of the lung is not uniform and that certain parts of it receive a larger amount of blood than others. Furthermore, it is believed by this investigator that the ligation of one particular artery merely shifts the mass of the blood into the still opened vessels, thereby retaining a normal pulmonary flow. Consequently, the right ventricle cannot be overtaxed in any appreciable measure, because the excess amount of blood is directed into those channels which normally possess a small blood stream. Tigerstedt admits, however, that this explanation is purely hypothetical.

Yas Kuno (9) has repeated these tests upon the "heart lung preparation," artificially perfused as advocated by Fühner and Starling (10). The pressures were measured in the aorta, the vena cava, the pulmonary artery and the left auricle. The results of these experiments show that the compression of the principal branches of the pulmonary artery does not affect the carotid pressure as long as the circulation is carried on under relatively low degrees of pressure. Contrariwise, a high degree of general pressure permits this procedure to depress the carotid pressure considerably, after which it again rises, although it never regains its previous level.

Because of the practical importance attached to this question I have subjected it to a reëxamination at the hand of exact quantitative data pertaining to the venous inflow into the heart. The experiments which are the topic of this memoir were performed upon etherized cats, weighing between 3.6 and 5.8 kgm. The skin having been reflected from the right lateral aspect of the thorax, an opening was made in the chest wall by the resection of the ventral portions of three or four consecutive ribs. Artificial respiration having been instituted, a screw-clamp attached to a long handle was applied to either the right or left lung at its hilum. This clamp remained in position throughout the experiment, care having been taken to prevent its pulling upon the vessels.

In a number of additional animals, the pulmonary artery was carefully isolated from the neighboring tissues in order to permit the application of clamps of similar construction to its left antero-superior and middle branches. The carotid artery was then connected with a mercury manometer. The venous inflow into the heart was registered by means of a recording stromuhr (11), inserted into either the inferior or superior vena cava, preferably the latter, because, as will be shown later, it gives lodgment to a larger amount of blood than the superior cava.

The inferior vena cava was made accessible to this instrument immediately below the pericardial sac by separating it from the right phrenic nerve and a small adjoining strand of fatty tissue. An artery clip was then applied to it about 2 cm. above the diaphragm, and another at the point where it gives attachment to the pericardium. The cannulas of the stromuhr were usually in their proper positions within 3 minutes after the interruption of the blood flow. During the interim the heart was supplied with what appeared to be a sufficient amount of blood through the superior vena cava and the vena azygos. Naturally, the adequacy of its supply could only be ascertained in a relative way; i.e., by the fact that the shutting off of the inferior caval blood for so brief a time did not materially weaken its beat. Furthermore, any decrease in the force of its contractions was rectified almost immediately after the clips had been removed from the inferior cava.

The temporary stagnation of the blood in the inferior cava usually gives rise to a considerable fall in the aortic pressure. This fall, however, could be avoided by applying an artery clip to the thoracic aorta very shortly before the occlusion of the inferior cava. At all events, this vascular depression quickly righted itself as soon as the inferior cava was allowed to discharge its contents into the heart in the normal way. This adjustment revealed itself most clearly by the fact that the arterial and venous pressures retained relatively normal values throughout these experiments. In the few instances in which accidental bleeding had established a rather low arterial pressure, a few cubic centimeters of normal saline solution were first allowed to enter the heart through a special lateral tube attached to the stromuhr. The cannula inserted in the central end of the vena cava was connected with a membrane manometer of the Hürthle type. Thus the record of each experiment embraces the tracing of the carotid blood pressure in relation with the curve of the pressure prevailing in the inferior vena cava. In addition, it shows the calibration of the venous blood stream, as well as the abscissa for the pressures and the second-marks of a Jacquet chronograph.

A signal was added at times to be able to indicate the beginning of the procedure to be tested.

TABLE 1

Changes in the blood flow in the inferior vena cava following the compression of the superior branch of the pulmonary artery

Experiment 4; cat: 4.1 kgm., heart: 27 grams; frequency: 180 per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Carotid artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm. Hg*	*mm. Hg*	
7	5.0	19.8	3.96	106.4	1.0	Normal
8	4.9	20.5	4.16			
9	5.0	20.0	4.00			
10	5.0	20.2	4.04			
Average.....			4.04	106.4	1.0	
11	5.2	19.5	3.75	105.0	1.5	Compression left superior branch of pulmonary artery
12	5.5	20.0	3.63			
13	5.6	20.1	3.59	90.2		
14	5.8	20.0	3.44		2.0	
15	5.7	19.8	3.47			
16	5.7	20.2	3.54	91.5		
17	5.7	20.0	3.50			
18	5.7	20.0	3.50			
19	5.9	19.8	3.35	90.5		
20	5.8	19.8	3.41			
21	6.0	20.2	3.36			
22	5.8	20.0	3.44			
23	5.3	20.0	3.77	95.6		Compression removed
24	5.0	20.2	4.04	105.0	1.0	
25	5.0	20.2	4.04			
26	4.8	20.0	4.16			
27	5.0	19.8	3.96			

The procedure with which we are more particularly concerned at this time, is the temporary compression of the left superior branch, left middle branch, and entire left or right pulmonary artery. The experimental conditions were kept uniform throughout these tests. Thus the pulmonary ventilation was adjusted at a constant level, yielding a moderate

expansion of the lungs. The procedure followed in each case consisted in obtaining a sufficiently large number of stromuhr-phases from which the normal flow and pressures could be calculated. Then followed the compression, lasting anywhere from 1 to 5 minutes, and accomplished by closing the clamp which had previously been applied to the vessel. Subsequent to the compression, the stromuhr was again allowed to register a series of normal phases before the aforesaid procedure was repeated. Several tests were made in the course of each experiment, the total time consumed by them being about 20 minutes.

These experiments clearly prove that the results of Lichtheim and R. Tigerstedt are incorrect. Even the blocking of a single superior branch sufficed to evoke unmistakable changes in the arterial and venous pressures as well as in the caval blood flow. The character of these changes may easily be followed with the help of the data given in table 1. These values were obtained in a cat weighing 4.1 kgm. and yielding a carotid pressure of 106.4 mm. Hg. A glance at this outline will show that the exclusion from the circulation of the superior lobe induced a fall in the carotid pressure amounting to 14.2 mm. Hg. To be sure, this is not a significant change, but since the question at issue really is whether such a decrease in pressure takes place at all, it must certainly be answered in the positive. Furthermore, this decrease was not compensated for in the course of these tests, lasting anywhere from 1 to 5 minutes. This result is not in harmony with the statement of Yas Kuno, implying that the fall in aortic pressure following the ligature of one lung, lasts for only 13 to 18 heart beats. It will be remembered that this investigator employed "heart-lung preparations" and hence instituted conditions which cannot be regarded as normal.

The venous pressure, measured in the inferior vena cava near the right auricle, suffered an increase which, although slight in all cases, was nevertheless clearly recognizable. In the record now under consideration it amounts to 1.0 mm. Hg. Entirely in harmony with these changes in the pressures, the venous supply of the heart invariably presented a significant reduction. In the example here given it amounts to 0.69 cc. of blood per second. Naturally, this decrease pertains solely to the blood flow in the inferior vena cava, but it may rightly be assumed that the flow in the superior vena cava is affected in a corresponding manner and measure. Several later calibrations of the inflow from the superior cava under identical conditions have proven this assumption to be correct. So far, however, I have not ascertained the blood stream in both venae cavae simultaneously, because the technical difficulties connected with experiments of this kind are very trying.

Regarding the changes evoked by the compression of the middle branch of one lung nothing further need be said, because they differ from

TABLE 2

The effect of compression of the vessels of the right lung upon the flow in the inferior vena cava

Experiment 17; cat: 4.5 kgm.; heart: 22 grams; frequency: 175 per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Carotid artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
21	3.4	20.0	5.88	98.7	1.2	Normal
22	3.6	20.0	5.55			
23	3.4	19.6	5.76			
24	3.6	19.8	5.50			
25	3.5	19.8	5.65			
26	3.6	20.0	5.55			
Average			5.64	98.7	1.2	
27	4.1	20.0	4.87	78.8	2.3	Compression of blood vessels of right lung
28	5.0	20.2	4.40	78.4		
29	4.6	20.0	4.34			
30	4.6	19.8	4.30			
31	3.5	20.0	5.77	102.5	1.5	Normal
32	3.6	20.2	5.61	96.5		
33	3.8	20.2	5.31	88.2		
34	3.4	20.0	5.88	86.0		
35	4.0	20.2	5.05		1.2	
36	4.5	20.0	4.44	74.2		Compression repeated
37	4.9	20.0	4.08			
38	5.0	20.0	4.00		1.5	
39	5.5	20.0	3.63	72.6		
40	4.0	19.8	4.95	96.4		Normal
41	3.7	19.8	5.37	93.2	1.2	
42	3.2	20.0	6.25	90.4		
43	3.4	20.0	5.88	98.6		
44	3.4	20.0	5.88			

those just described merely in their conspicuousness and not in their general character. Of much greater interest to us at this time are those hemodynamical changes which follow the exclusion from the pulmonary

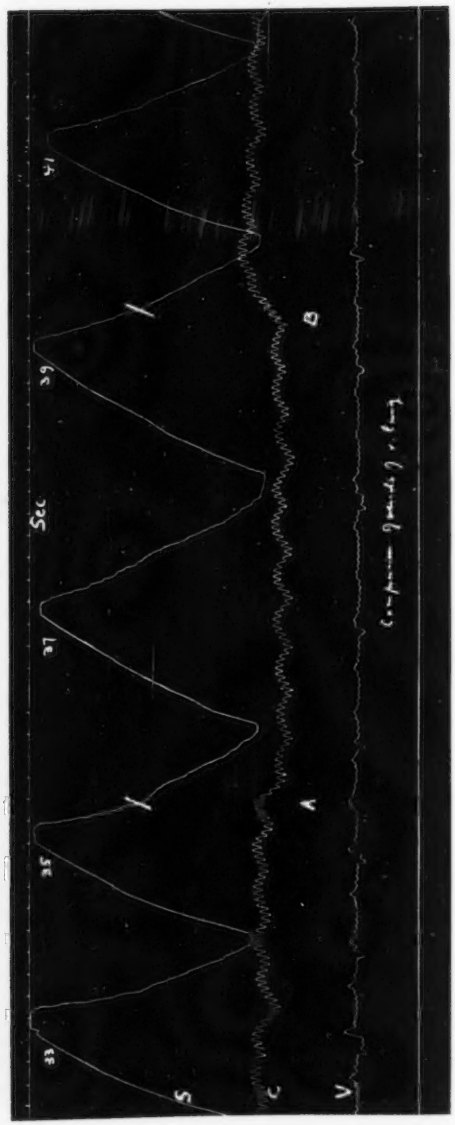

Fig. 1

circuit of one entire lung. This discussion may again be considerably abbreviated by referring more particularly to a single record, representing in a fair way the many tests that have been made to solve this question. I select for this purpose a section of the curve belonging to experiment 17 and embracing certain phases during which the vessels of the right lung were compressed at the hilum of this organ. The weight of this cat was 4.5 kgm. and that of its heart 22 grams. The values given in table 2 are directly transferable to figure 1, representing the second of these tests.

It is evident that this procedure leads to an almost immediate decrease in the carotid pressure which becomes fully established within about 2 seconds after the beginning of the compression and persists practically as long as the lung is excluded from the circulation. On releasing these vessels the general arterial pressure rises very rapidly, even exceeding its normal value for a brief period of time until compensated for by vasomotor changes. These fluctuations are frequently noted when the blood is suddenly shifted from one circuit to another in a mechanical way. It is to be noted, however, that the exclusion from the circulation of other organs such as the kidneys invariably produces a rise in the systemic blood pressure, because the blood previously allotted to these glands must now be accommodated in the general vessels. It is evident that the lungs occupy an entirely different position in this regard, because they lie in the direct path of the arterial supply, and the exclusion of one cannot be compensated for by a corresponding enlargement of the vessels of the still active organ.

The effects of this block can be overcome in a measure by increasing the frequency and capacity of the heart. Changes of this character, however, did not develop in the time allowed for these tests, and hence, we observe here a decided retardation in the venous inflow into the heart which is associated with a rise in the venous pressure. All these changes are clearly betrayed by the records now under consideration. Thus figure 1 shows a normal flow in the inferior cava of 5.05 cc. in a second, which gives way during the compression to one of 3.63 cc. in a second. The venous pressure increased during the first test from 1.5 to 2.3 mm. Hg, but only very slightly during the second. The carotid pressure decreased from 98.7 to 78.4 mm. Hg in the first instance, and from 86.0 to 72.6 mm. Hg in the second.

How closely these experimental conditions approach those noted in a person after the establishment of a pneumothorax is difficult to tell, because a collapsed lung may still permit a certain amount of blood to

pass and thereby compensate in a measure for the otherwise much greater reduction in the size of the pulmonary blood bed. (See page 239.) Secondly, a collapsed organ may in time become at least partially functional, thereby mitigating the immediate effects of the pneumothorax. The early clinical picture of this condition, however, includes at least two of the changes alluded to above. The question of whether an increased ventilation of the lungs actually favors the circulation through these organs, will be more fully considered in the succeeding paragraphs.

2. *The effect of varying degrees of ventilation of the lungs.* In accordance with the statements of Heger and Spehl (12) it is now generally believed that the difference in the amount of blood present in the lungs on inspiration and expiration is inconsiderable. R. Tigerstedt places this difference at only one-sixtieth of the total quantity, and assumes therefore that the ligation of a lung in the state of pneumothorax cannot produce a change materially different from that evoked by its ligation when in an expanded condition. It appears that the employment of rhythmic artificial respiration cannot make an appreciable difference in the results of experiments of this kind, in spite of the fact that the conditions of pressure are reversed (13). Thus, it is a well-known fact that the inflation of the lungs causes the arterial pressure to fall, whereas their deflation permits this pressure to rise. Evidently, the influx of the air occasions a compression of the pulmonary blood vessels, chiefly the alveolar capillaries, while the succeeding elastic recoil of the lungs reduces this pressure and hence also the resistance placed in the path of the blood ejected by the right ventricle. As has been stated above, the development of these changes in a direction the reverse of normal need not deter us from performing these experiments, because we are dealing here with the total venous supply of the heart under practically constant conditions. The question to be decided concerns itself with the possible changes in the pulmonary blood stream which are directly referable to variations in the expansion or ventilation of the lungs. If such changes actually develop during artificial respiration, we have every reason to believe that they also arise when the lung is expanded in a normal way or suffers a reduction in its volume in consequence of any factor interfering with the movement of the respiratory air.

As stated, these experiments were performed during rhythmic artificial respiration. The right side of the chest was widely opened. The right bronchus was then isolated and placed in a loose ligature, so as to be able to compress it at any time during these tests by means of a clamp fastened to a long handle. A small perforation was made in the wall of

this bronchus distally to the clamp. It was closed immediately with a small artery clip. This arrangement enabled me to impart to this lung any desired state of collapse, while the organ on the opposite side continued to receive the rhythmic currents of air. In order to prevent the over-distention of the left lung during the collapse of the right, the air was conducted through a large bottle possessing three outlets. Two of these served for the passage of the air, while the third was equipped with an adjustable screw-clamp. Any increase in the distention of the lung could thus be immediately corrected by enlarging this outlet.

Contrary to the theoretical considerations of R. Tigerstedt, these experiments show that the venous supply of the heart and, therefore, also its output is markedly affected by the activity of the lung. The most efficient flow was obtained when this organ was retained in a state of distention equalling that of its normal expansion. It may be said that this degree of inflation which is designated in the succeeding protocol of experiment 39 as "medium" (table 3), imparted to this organ a volume sufficient to fill the cavity of the chest when increased to its inspiratory size. At this time the carotid pressure as well as the venous pressure and flow attained their highest values.

All greater degrees of ventilation led to a reduction in the venous supply of the heart, a rise in the venous pressure, and a fall in the carotid pressure. Furthermore, these changes preserved a direct relationship to the force of the air-current. In the examples given in table 3, the flow in the inferior vena cava during the "medium" inflation of the lungs, amounted to 7.45 cc. in a second. The carotid pressure equalled 92.0 mm. Hg., and that in the inferior cava 1.0 mm. Hg. When the lungs were inflated in a measure causing their tips and borders to advance well beyond the edges of the opening in the wall of the chest, the venous inflow decreased almost immediately to 3.44 cc. in a second, i.e., to about one-half of normal. The carotid pressure decreased at this time to 68.5 mm. Hg., while the venous pressure rose to 6.5 mm. Hg.

This degree of inflation is characterized in the protocol of experiment 39 as "strong." It appears, therefore, that the delivery of a large amount of air invariably results in an "inspiratory" retardation of the venous inflow and a very decided rise in the venous pressure and fall in the carotid pressure. The general character of these changes immediately recalls to our minds the fact that the size of the pulmonary blood bed is decreased during the period of inflation, causing the resistance in this circuit to be increased. Consequently, the decrease in the venous supply of the heart here observed is referable to a mechanical hindrance to the blood flow through the lungs.

TABLE 3

The effects upon the blood flow in the inferior vena cava of varying degrees of ventilation of the lungs

Experiment 39; cat: 4.6 kgm.; heart: 24 grams; frequency 180 per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Carotid artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
5	2.6	19.5	7.50	92.0	1.0	Normal; medium inflation
6	2.8	19.5	6.96			
7	2.5	19.8	7.92			
8	2.6	19.8	7.61			
9	2.8	19.8	7.07			
10	2.7	19.6	7.25			
11	2.5	19.6	7.84			
Average.....			7.45	92.0	1.0	
12	3.5	19.6	5.60	82.5	4.0	Strong inflation
13	3.8	19.6	5.15	75.0	6.0	
14	4.0	20.0	5.00			
15	3.6	20.0	5.55			
16	4.0	20.0	5.00	70.8		
17	3.8	20.0	5.26			
18	3.1	20.0	6.45	90.6	1.0	Medium inflation
19	2.8	20.0	7.14			
20	2.8	19.8	7.07			
21	2.5	19.8	7.92			
22	2.5	20.0	8.00			
23	2.6	20.0	7.68			
24	4.6	19.8	4.30	75.5	5.0	Strong inflation
25	4.8	19.8	4.12		6.5	
26	5.0	19.8	3.96			
27	5.0	19.8	3.96	68.5		
28	5.5	20.0	3.63			
29	5.6	20.0	3.57	62.5		
30	5.8	20.0	3.44			
31	4.0	20.0	5.00	90.0	1.0	Medium inflation
32	2.6	20.0	7.68			
33	2.7	19.8	7.33			
34	2.7	19.8	7.33			
35	2.6	19.8	7.61			
36	2.6	19.8	7.61			

Even a very casual inspection of the curve represented in figure 2 will leave no doubt as to the correctness of the interpretation of these results. This figure represents the phases 52 to 65 of experiment 39. It is noted that the change from the "medium" to the "strong" inflation (at *A*) gives rise to a very abrupt fall in the carotid pressure, *C*, and a very decided increase in the amplitude of the respiratory variations in the arterial blood pressure. The venous pressure, *V*, is increased and presents equally decisive changes in pressure. As has been mentioned above, the arterial pressure falls during the inflation, while the venous pressure rises. The amount of blood delivered in this case to the heart equals 7.12 cc. in a second during "medium" inflation, but only 3.96 cc. in a second during "strong" inflation. It is to be noticed especially that the curve of the bloodflow presents definite fluctuations. Those indicated by the letters *CD* signify a very decided reduction in the venous supply. If these ordinates are now compared with those indicating the periods of inflation and deflation upon the curves of the pressures, it will be found that the phases of markedly decreased flow coincide with the states of inflation of the lung. In the figure now under consideration, the inflow amounts to only 0.06 cc. in a second during this period, and to 7.85 cc. in a second during the deflation. Accordingly, it cannot be doubted that the excessive distention of the alveoli hinders the flow through the capillaries traversing their walls.

The amplitude of these fluctuations decreased very perceptibly when the volume of the air delivered was diminished. As has been stated above, the best results were obtained when the lungs were subjected to only a "medium" degree of distention. A slighter inflation than this did not materially alter the flow nor the pressures. In other words, between the "medium" and "minimal" positions of the lungs a significant difference in the inflow could not be noted.

The experiments cited in the first section of this paper have shown that the compression of the pulmonary vessels of one side gives rise to a decided reduction in the venous supply of the heart, a rise in the venous pressure and a fall in the carotid pressure. Likewise, the experiments just described prove that these hemodynamical factors change with the state of activity of the lungs. The question still to be decided concerns itself with the vascularity of the collapsed lung as against that of the ligated organ. R. Tigerstedt maintains that the blood flow through a lung after the establishment of pneumothorax cannot differ materially from that of a functioning one. This theoretical contention is in part disproved by the preceding experiments.

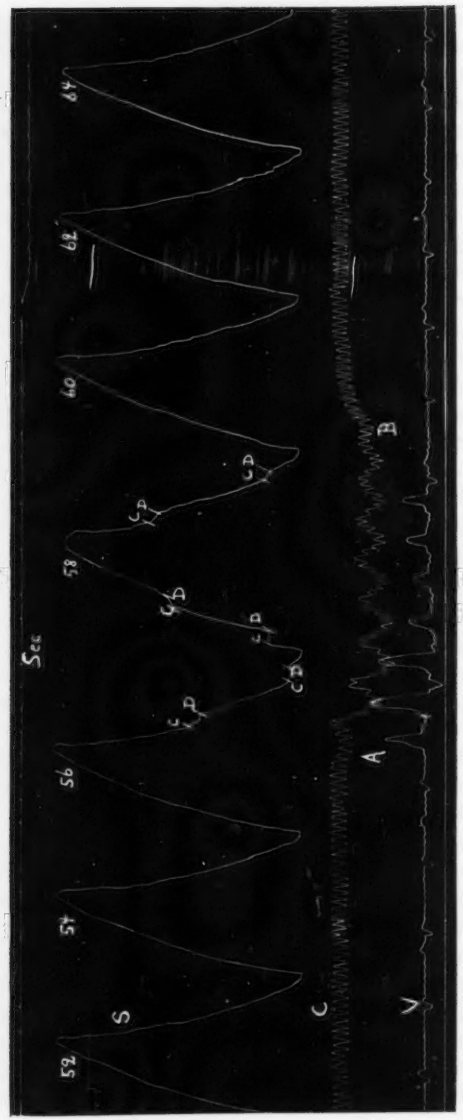

Fig. 2

Yas Kuno has attempted to solve this question by ligating the pulmonary vessels during the respiring and collapsed states of the lung. But in spite of many attempts, this investigator admits that he is not in a position to give a satisfactory answer to this question, because the results of ligature of one lung are not always quantitatively the same, and because the difference in the results obtained from the ventilated and collapsed lung respectively is not large enough to be decisive. At the hand of the preceding calibrations of the venous inflow it is now readily seen that this must necessarily be so. These calibrations lead us to infer that the pulmonary flow remains practically the same as long as the lungs are kept in a position intermediate between "minimal" and "medium" activity.

Having established this fact, a number of experiments were performed during which the right bronchus was temporarily clamped, while the air within this lung was allowed to escape through a small perforation in its wall. The records show that this procedure gives rise to only a minimal reduction in the venous supply of the heart, a very slight rise in the venous pressure, and an equally insignificant change in the carotid pressure. Contrariwise, the subsequent ligation of the vessels of the collapsed lung led to very decisive changes of this character.

Accordingly, it must be concluded that the simple collapse of one lung does not seriously impair the total blood flow through the lungs. Hence, the vessels of the collapsed lung must permit an almost normal quantity of blood to pass. A clear distinction should, therefore, be made between a lung in the state of simple collapse and one the vessels of which have been ligated. The former still possesses a considerable vascularity. This fact furnishes a satisfactory explanation for the many divergent views and explanations which have been embodied in the literature pertaining to this subject-matter.

3. *Partial and total compression of the pulmonary artery. Pulmonary stenosis.* Upon the basis of the preceding results, showing that the occlusion of even a relatively small branch of the pulmonary artery evokes an unmistakable retardation in the venous return to the heart, it may be assumed that the partial compression of the principal supply vessel of the lungs must produce very similar although more decisive changes. This assumption is fully substantiated by the experiments to be described in the succeeding paragraphs. In addition, these tests permit us to obtain a concise idea regarding the extent of the constriction required to induce a failure of the circulation. It is obvious that the artificial compression of the pulmonary artery may be employed to

imitate those inherited and acquired lesions of the pulmonary valve which constitute the condition of stenosis of this cardiac orifice.

In order to be able to diminish the size of the pulmonary artery in a circular manner and to be able at the same time to estimate the degree of the constriction, a clamp of the following construction was made use of.

A ring of metal, measuring about 12 mm. in diameter and possessing perfectly smooth edges, was cut in two. Its halves were then soldered to the blades of a scissor-like instrument in such a way that they overlapped and their free tips were turned toward one another (fig. 3). By closing this instrument the central opening may be decreased to any size desired. A safety spring holds the blades in this position. Furthermore, a scale attached to one of the handles permits the experimenter to ascertain the degree of compression, as previously determined by tests upon the excised vessel.

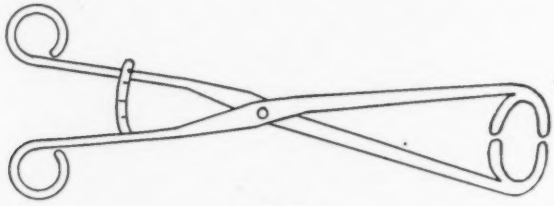

Fig. 3

Inasmuch as the root of the pulmonary artery is closely adherent to the wall of the left auricle and arch of the aorta, the blades of this instrument were applied about 1.5 cm. distally to the semilunar cusps. In other respects the procedure here followed remained the same as that described in a preceding section of this paper. Having ascertained the normal flow and pressure in the inferior or superior vena cava, the lumen of the pulmonary artery was constricted for a varying period of time. Its size was reduced at different times to three-fourths, one-half, and one-fourth of normal. A number of experiments were also made to determine the effects of the total occlusion of this artery.

I insert in this place table 4 which embraces the protocol of a limited number of phases of experiment 26 during which the lumen of this vessel was reduced at intervals to three-fourths and one-half of normal. It will be seen that this procedure leads to a reduction in the venous return, an increase in the venous pressure and a fall in the carotid pressure. Although qualitatively the same as those produced by the compression

TABLE 4

The effects of stenosis of the pulmonary orifice upon the blood flow in the inferior vena cava

Experiment 26; cat: 4.7 kgm.; heart: 25 grams; frequency: 188 beats per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY OF BLOOD	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Carotid artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
14	3.2	19.8	6.18	102.6	1.0	Normal
15	3.3	19.8	6.00			
16	3.5	19.8	5.65			
17	3.0	19.8	6.60			
18	3.2	19.8	6.18			
Average.....			6.12	102.6	1.0	
19	4.0	19.8	4.95	94.6	2.5	Size of lumen reduced to three-fourths of normal
20	3.8	20.0	5.26			
21	3.8	20.0	5.26			
22	4.1	20.2	4.92			
23	4.1	20.2	4.92	92.5	3.0	
24	4.0	20.2	5.05			
25	3.5	20.2	5.77	102.0	1.0	Normal
26	3.3	20.2	6.06			
27	3.3	20.0	6.06			
28	3.4	20.0	5.88			
29	3.4	20.0	5.88			
30	3.4	20.0	5.88			
31	4.1	20.0	4.87	75.6	5.0	Size of lumen reduced to one-half of normal
32	4.1	19.8	4.82	63.5		
33	5.0	19.8	3.96			
34	5.0	19.8	3.96	63.0	10.0	
35	5.5	19.8	3.41		10.5	
36	6.5	20.0	3.07			
37	6.0	20.0	3.33			
38	3.4	19.8	5.82			Normal
39	3.2	19.8	6.18	100.5		
40	3.0	20.0	6.45		1.0	
41	3.1	20.0	6.45			
42	3.2	20.0	6.18			

of the vessels of one lung, these changes eventually assumed a much greater amplitude. It is to be noted, however, that a diminution of the caliber of this vessel to three-fourths of normal is well compensated for. More serious consequences result only after the stenosis has been increased to one-half of the normal lumen of this vessel. The venous pressure then rose from 1.0 mm. Hg to 10.5 mm. Hg, while the venous supply was reduced close to one-half of normal. The carotid pressure was decreased by about 40 mm. Hg. In general, however, it may rightly be stated that a moderate stenosis is readily balanced so that a failure of the circulation cannot be expected to result until the size of this orifice has been diminished to at least one-half of normal. These facts strongly suggest that the compensation is ample and is tenaciously kept up until a relatively severe stenosis has been established. A failure of the circulation set in as a rule after the size of the pulmonary orifice had been diminished to about one-fourth of normal. The carotid pressure then decreased to less than one-half of normal, while the venous return assumed a value considerably less than one-half its normal one.

It is commonly believed that a backward flow in the veins is made impossible by the fact that the smaller venous orifices are guarded by valves which close immediately when the pressure in the central veins surpasses that prevailing in the more distal channels. It is true, however, that these venous valves are not present in the central portions of the venae cavae, and first appear at the points of entrance of the hepatic and jugular veins. The results of the total occlusion of the pulmonary orifice prove that the competency of the venous valves and, in fact, of the tricuspid valve, cannot be retained when the heart is made to act against so high a resistance. The insufficiency developing under these conditions leads to a regurgitation of the auricular blood and a backward flow in the central veins.

These facts may best be illustrated with the help of a curve such as is represented in figure 4. Previous to the complete occlusion of the pulmonary artery at *A* the flow in the inferior cava amounted to 5.00 cc. in a second. The carotid pressure equalled at this time 69.5 mm. Hg and the venous pressure 0.8 mm. Hg. Immediately upon the complete constriction of the pulmonary orifice, the bloodflow assumed a value of zero (*A* to *A1*), and then (*A1* to *B*) one of 1.2 cc. per second in the reverse direction, i.e., from the right auricle toward the liver. The total quantity of blood forced back during this brief compression amounted to 2.2 cc. Meanwhile the venous pressure rose from 0.8 mm. Hg to about 15.0 mm. Hg, while the carotid pressure moved rapidly toward zero.

Owing, however, to the general venous stasis, it diminished more rapidly at first than later on. Subsequent to point *B*, when the pulmonary artery was again opened, the pressures and the flow quickly resumed their normal values.

For the reason that I did not care to abbreviate any of these experiments by this means, I did not continue these complete compressions of the pulmonary orifice for a longer period than 30 seconds. The heart recovered its action in all these instances very promptly, although a prolonged constriction reduced its rate considerably. It is made evident by these tests that if the heart is forced to act against the closed pulmonary circuit, its right side finally expels its contents in the direction of least resistance, namely, into the central veins. Moreover, judging by the marked increase in the venous pressure and the magnitude of the backward flow, this action must be participated in by the right ventricle. Hence, the excessive strain placed upon the right ventricle must render the tricuspid valve incompetent. The final result of this backward discharge of the contents of the heart must be an equalization of the pressures and a simple to and fro motion of the blood which continues as long as the auricle responds.

In this connection brief reference should also be made to the assertion that the ventricles of the dog's heart may be distended until the pressure within them equals 200 to 250 mm. H_2O during diastole before regurgitation actually sets in. Evidently, these figures are intended to convey the idea that the intraventricular pressure must be raised excessively before these valve flaps cease to act properly. If an interpretation of this kind is placed upon them, which they do not merit, it is not in harmony with the more general belief that a relatively slight distention suffices to produce an incompetency of these valves. The foregoing experiments tend to confirm the latter view, because a reduction of the size of the pulmonary orifice to somewhat less than one-half of normal suffices to render the pulmonary valve at least slightly insufficient. It may also be inferred that the venous valves remain competent only as long as the pressures upon their two surfaces are not markedly different. The complete exclusion of the pulmonary circuit in the presence of a normally acting heart is one of the conditions which will cause them to become insufficient.

4. *The effects of tricuspid regurgitation.* An insufficiency of any of the cardiac valves is usually brought about by tearing the valve flaps or by disconnecting them by means of a long, hook-shaped knife from the chordae tendineae. On the right side, this instrument is inserted through

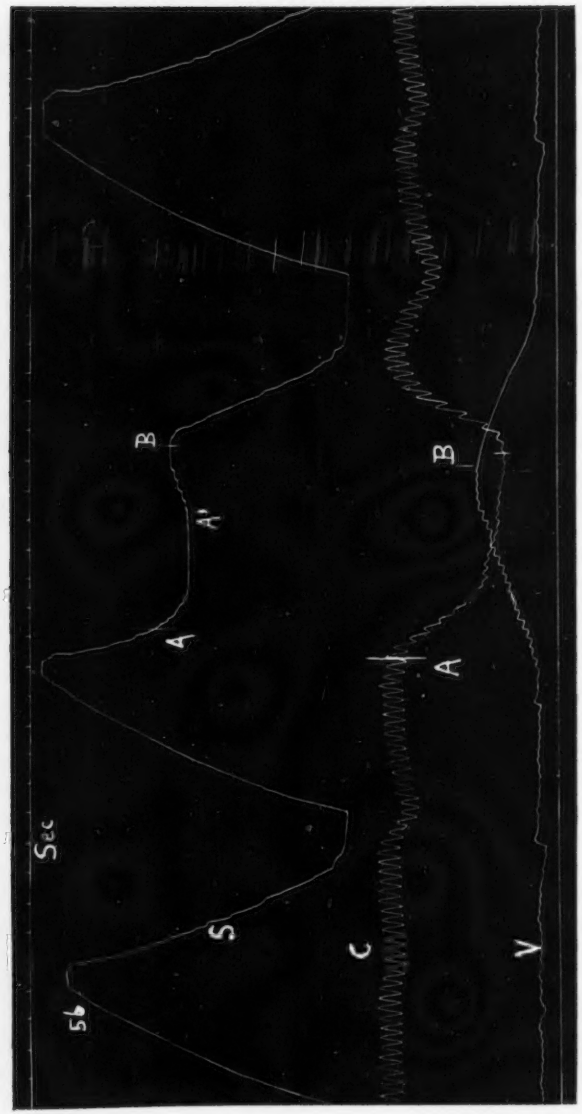

Fig. 4

the external jugular vein and, on the left side, through the carotid artery. Procedures of this kind have been employed by Becker (14), Klebs (15), Rosenbach (16), Rihl (17) and MacCallum (18). It is obvious that the tearing of the valve flaps presents no means of ascertaining the extent of the valvular insufficiency and renders a return to normal hemodynamical conditions impossible. In order to avoid these difficulties, I have devised a cannula which may be temporarily inserted between the valve flaps without lacerating them. It may be withdrawn at any time,

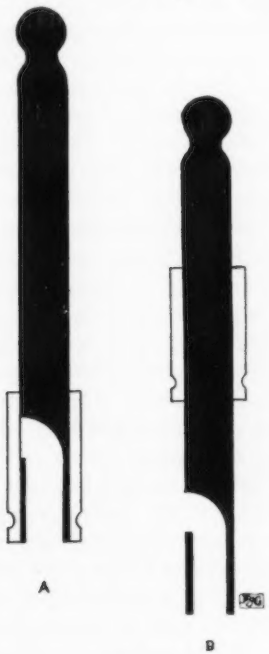

Fig. 5

thereby permitting the almost immediate reëstablishment of normal valve action (fig. 5).

This cannula consists of a short outer jacket of glass or metal, measuring 4 cm. in length and possessing an internal diameter of 5 mm. Its lower margin bears a groove, so that it may be firmly fixed in the wall of the auricular appendix by means of a ligature. Within this jacket is contained a tube, measuring 8 cm. in length and possessing an outer diameter of somewhat less than 5 mm. Its inner diameter measures

4 mm. The surface of the inner tube should be closely adjusted to that of the outer, so that the blood can not escape through this channel. It will be noted that the inner tube is solid for a distance of about 5 cm. Only its lower portion is left open, and bears a lateral orifice measuring about 4 mm. in diameter.

To begin with, the lower end of the inner tube is retracted into the jacket (*A*). The appendix of the right auricle is then temporarily shut off from the main cavity by an artery clip. The end of the cannula is now securely fastened in the wall of the appendix by means of a ligature. Having adjusted the cannula in a convenient position by allowing it to rest upon a plug of cotton, the artery clip is removed. When it is desired to establish the regurgitation, the inner cannula is moved downward until its orifice has progressed beyond the auriculo-ventricular groove, while its lateral outlet rests about midpoint in the auricle (*B*). Naturally, the cannula should be well oiled to retard coagulation and should be held in a median position between the walls of the orifice, so as to permit the margins of the flaps to form firm contact with its outer surface. It may be withdrawn into its former position at any time. Normal circulatory conditions are then established very rapidly.

A cannula of this size gives rise to a degree of regurgitation which produces a decisive rise in the venous pressure and very significant decrease in the caval blood flow. In all these tests the carotid blood pressure suffered a marked decrease. Naturally, we are dealing in this instance with the immediate effects of tricuspid regurgitation, such as result in the human heart during periods of lost compensation. It is obvious that the principal effect of a lesion of this kind is the venous stagnation. The fact that this central retardation also affects the peripheral circulation, has been emphasized repeatedly. Thus, Hooker and Eyster (19) have noted that the pressure in the veins of the arms of a person afflicted with tricuspid insufficiency may reach 26 cm. H_2O or about 20 mm. Hg. The present records show that the venous pressure may easily reach a height of 8 to 12 mm. Hg during the period of regurgitation, while the flow in the inferior vena cava assumes a value about two-thirds of normal. A corresponding decrease was noted in the carotid pressure. Ordinarily, these effects are compensated for in time by a hypertrophy of the right ventricle and an increase in the force of the heart beat (20). For this reason, and also because of the back pressure from the veins and capillaries, the systemic pressure cannot fall very markedly. Evidently, this is the usual condition during the period of compensation.

5. *The effects of aortic stenosis and mitral insufficiency.* The clinical picture of aortic stenosis embraces a relatively high arterial pressure (130 to 160 mm. Hg) which is occasioned by a greater pumping power of the left ventricle and a markedly increased intraventricular pressure. But in spite of its hypertrophic condition, the left ventricle is quite unable to eject its contents quickly, and hence, the pulse wave becomes slow in its ascent and is surmounted by a rounded apex. It is believed that the right side of the heart is not affected until much later, when the stage of decompensation sets in.

Since the hypertrophy of the left ventricle requires a relatively long time for its development, the present experiments were undertaken merely for the purpose of portraying in a feasible manner the immediate effects of the constriction of the aortic orifice. The results of this procedure, therefore, are comparable to those changes which arise during the stage of decompensation. They consist in a rise in the caval pressure, a reduction in the venous supply of the heart, and a marked fall in the carotid pressure. Obviously, the hindrance to the escape of the contents of the left ventricle gives rise to a retardation of the pulmonary flow and a diminished inflow into the right auricle. As in the case of pulmonary stenosis, these effects do not assume a serious character until the constriction has caused a reduction in the size of the aortic orifice to about one-half of normal. Beyond this point the circulation fails rapidly.

These experiments confirm the work of Luderitz (21) and de Heer (22), which stresses the fact that a mild degree of aortic stenosis is easily overcome by the ventricle and that the establishment of definite circulatory changes requires a constriction of considerable degree. De Heer's conclusions are based upon alterations in the volume-curve of the heart, registered in relation with the carotid and intraventricular pressures. A somewhat similar statement has been made by Cohnheim (23) who has sought to confirm it by simple measurements of the carotid pressure during compression of the arch of the aorta. Furthermore, it has been noted by MacCallum that if the arterial pressure is well maintained, the pulmonary pressure remains practically unaltered. Contrariwise, a decrease of the former is invariably associated with a rise of the latter. In amplification of this statement, the present experiments show that this effect of the back-pressure leads to a reduction in the output of the right ventricle, as is revealed by a diminution in the venous inflow into the right auricle and a rise in venous pressure. It is granted, however, that these changes are indicative of cardiac decompensation,

and do not betray themselves clearly until the aortic orifice has been constricted to one-half its normal size.

The establishment of a mitral insufficiency by the method previously applied to the tricuspid valve, has not led to results materially different from those noted by MacCallum and McClure (24). It is well known that the production of a lesion of this kind in an artificial circulation machine evokes a rise in the left intra-auricular pressure and a fall in the systemic arterial pressure. These changes are due in all probability to the decrease in the output of the left ventricle, and may readily be compensated for by a more frequent and forceful compression of the bulb and a narrowing of the capillary outlet. Clinical observations have proved that similar alterations result in the human circulation which tend to keep the flow through the lungs near normal. In this connection, it should also be remembered that the intra-auricular pressure does not rise materially until the regurgitation has assumed a relatively severe character (25).

The present experiments have yielded a retardation of the flow through the lungs and a decrease in the output of the right ventricle, as revealed by a diminution of the venous inflow into the right auricle and a rise in the caval pressure. They do not fully confirm the rather general view that lesions of the mitral valve must be severe before they can affect the circulatory conditions in the right side of this organ and the central veins.

6. *The effects of compression of the vessels of the head upon the blood flow in the inferior vena cava.* These experiments are concerned with the effects of the exclusion of different circuits of the vascular system in order to be able to obtain an accurate measure of the volume of the blood stream in the inferior cava as against that in the superior cava. They consist essentially in attempts to direct the total mass of the blood through either vena cava. Thus, the calibrations upon the inferior cava were carried on before as well as after the vessels of the head had been compressed at a point about 1 cm. distant from their origins from the arch of the aorta. In a second series of experiments the flow through the superior vena cava was ascertained normally as well as subsequent to the occlusion of the arch of the aorta distally to the orifices of the aforesaid arteries of the head region.

Before entering upon a discussion of the results of these experiments, brief reference should be made to a series of tests performed to determine the changes in the blood flow through the superior cava after the compression of the inferior cava, and in that through the inferior cava subsequent to the occlusion of the superior cava. I had supposed that the

inflow through the superior vessel would be greatly augmented after the constriction of the inferior vena cava above the diaphragm. Likewise, I had assumed that a similar change would develop in the inferior cava after the occlusion of the veins of the head region. Both suppositions could not be substantiated experimentally. The reason for this is not difficult to find, because since the carotid pressure decreased very markedly after the occlusion of the inferior vena cava, the carotid and subclavian systems must have been deprived of the pressure required to propel an adequate amount of blood through the superior cava. In consequence of this decrease in the venous return, the heart weakened perceptibly. It will be shown later that the venous supply derived from the superior cava is considerably smaller than that obtained from the inferior cava. It is evident, however, that the decrease in the inflow from the superior cava and resultant fall in the venous pressure are occasioned by an engorgement of the vessels tributary to the inferior cava. A very large proportion of the total amount of the circulating blood is stagnated in the circuits of the thoracic aorta, thereby depriving the subclavian and carotid arteries of their normal quantity of blood. Very similar effects were noted in the inferior vena cava after the ligation of the superior vena cava, but owing to the relative smallness of this circuit, these changes were not so decisive as those obtained by blocking the inferior cava.

The results obtained by the compression of the corresponding arterial supply channels were very different from the preceding. This fact may be illustrated by a brief study of the changes evoked in the circulation of the inferior vena cava in consequence of the occlusion of the arteries of the head. I insert in this place the protocol of two tests, belonging to experiment 29 (table 5). The first of these is reproduced in figure 6. It will be noted that the blood flow in the inferior cava is very decisively increased by the compression, and that equally conspicuous rises have taken place in the arterial and venous pressures. Thus, we find here a normal flow of 2.94 cc. in a second contrasted against one of 5.00 cc. in a second subsequent to the constriction of the vessels of the head and forelegs. The rise in the caval pressure to 5.6 mm. Hg is associated with one of about 80 mm. Hg in the arterial pressure measured in the femoral artery.

These experiments permit us to form an approximate idea regarding the total venous supply of the heart, because the occlusion of the circuits of the head and forelegs forces practically the entire output of the left ventricle into the tributaries of the inferior cava. An exception is formed by that portion of it which traverses the intercostal arteries and is

finally returned to the heart by way of the vena azygos. The occlusion of this vessel near the confluence of the venae cavae did not result in a material increase in the flow through the inferior cava. At best it

TABLE 5

The effects upon the blood flow in the inferior vena cava of compression of the arteries of the head and forelegs

Experiment 29; cat: 3.8 kgm.; heart: 18 grams; frequency: 146 beats per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY OF BLOOD	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Femoral artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
13	6.5	19.8	3.04	75.6	1.2	Normal
14	6.3	19.8	3.14			
15	6.0	20.0	3.33			
16	9.0	20.0	2.22			
17	6.6	19.8	3.00	74.3		
Average.....			2.94	74.3	1.2	
18	8.2	19.8	2.41	119.4		Compression of vessels of head and forelegs
19	4.1	20.0	4.87	161.2	5.6	
20	7.1	20.0	2.81	160.5		
21	3.9	19.5	5.00	120.1	5.0	
22	6.9	19.5	2.82	63.1	1.5	Normal
23	7.4	19.8	2.67	62.6		
24	7.0	19.8	2.82			
25	7.0	19.8	2.82	70.5	1.2	
26	4.0	19.8	4.95	89.2		Compression of vessels of head and forelegs
27	3.2	19.8	6.19	155.4	6.5	
28	3.0	19.8	6.60	162.8		
29	3.6	19.8	5.50	162.0	6.0	
30	3.4	19.8	5.82	162.0		
31	6.5	20.0	3.07	74.5	1.2	Normal
32	6.4	20.0	3.12			
33	6.5	20.0	3.07	72.4		

amounted to only 0.3 cc. in a second. Making allowance for this difference it will, therefore, be observed that the maximal caval supply of the heart of this animal amounted to 5.3 cc. in a second or to about 318 cc. in

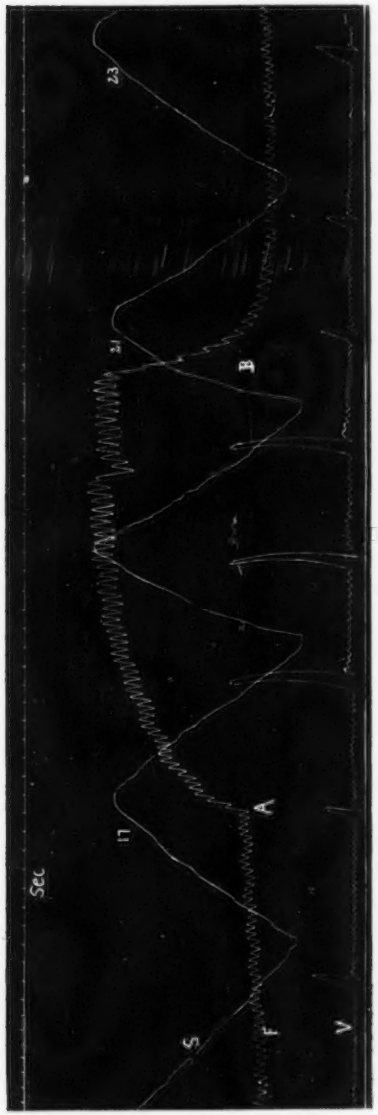

Fig. 6

a minute. If these values are now compared with the frequency of this organ of 146 beats per minute, it will be noted that the right auricle received 2.1 cc. of caval blood during every diastole. The weight of this animal was 3.8 Hg, and that of its heart, 18 grams.

Naturally, a computation of the entire discharge of the right ventricle cannot rightly be made from these figures, because the inflow from the coronary sinus is not known and cannot, therefore, be included in this calculation. The inflow from the venae cavae, however, must correspond to the blood stream in the aorta distally to the orifices of the coronary arteries. Leaving out of consideration the blood stream in the coronaries, it may then be said that the general tissues of this animal received about 318 cc. of blood in a minute. Thus each kilogram of substance received about 84 cc. of blood per minute or 0.84 cc. per gram.

It has been shown, however, that the blood is distributed to the different tissues in very unequal amounts; those forming the framework of the body receiving much less than those undergoing intense metabolic changes. I insert the preceding figures merely to show that the ventricular output of the cat's heart is very small, and does not even approach that of the dog's heart provided our general estimates (30 to 40 cc. per beat) of the pumping power of the latter organ are at least approximately correct. I personally do not concur in the view that the ventricular output of a dog weighing about 15 kgm. possesses so high a value. The smallness of the output of the cat's heart is compensated for by its greater frequency. It is true that the weight of the animal upon which this calculation is based is rather small, but this factor is not of decisive value, because the succeeding composite figures of the blood flow in the two venae cavae will show that a heart weighing about 20 grams does not discharge more than 3.5 cc. of blood per beat when the arterial pressure equals 100 mm. Hg. Furthermore, if the total amount of blood present in this cat is calculated at 7 per cent of the body-weight, the circulation-time for the greater circuit must amount to about 35 to 40 seconds. This value is in close agreement with the figures published in more recent years.

The measurements of Joseph (26) have demonstrated that the ratio between the weight of the heart and that of the body varies in cats between 4.56 and 4.58 grams per kilo. My own figures agree satisfactorily with these. Likewise, R. Tigerstedt (27), who inserted a stromuhr in the aorta of a rabbit, has obtained an output varying between 1.04 and 2.41 cc. per second, or between 0.36 and 0.83 cc. per beat in a rabbit weighing about 2.0 kgm. If an allowance is made for the

greater weight of cats, the present experiments have yielded results which satisfactorily agree with these.

7. *The effects of compression of the thoracic aorta upon the blood flow in the inferior vena cava.* It has been stated by Mall (28) that the occlusion of the aorta immediately beyond the origin of the left subclavian artery renders the circuits below the diaphragm absolutely bloodless. The crural artery will then always be found free from blood. Contrariwise, the compression of the aorta immediately above the diaphragm still permits a small portion of blood to enter the abdominal vessels. Inasmuch as in the former instance the stimulation of the greater splanchnic nerve evoked a rise in the carotid pressure, Mall assumed that this rise was due to a transfer of venous blood from the constricting portal vein. Accordingly, this investigator concluded that this vein is supplied with vasomotor nerves, a contention which has been disproved by Burton-Opitz (29). Furthermore, Vehlich (30) has stated that the compression of the aorta distally to the left subclavian artery does not entrap the blood in the anterior channels of the body, but favors the opening up of a very efficient system of anastomosing vessels. One of these channels of communication is furnished by the arteria spinalis anterior (31).

This assumption of Vehlich is in entire agreement with the observations of Hering (32) and Heidenhain (33), proving that the crural artery cannot be rendered absolutely bloodless by the ligation of the aorta. The existence of an anastomosis between this vessel and those of the posterior part of the body is also made probable by the experiments of Basch and Oser (34) as well as by those of Pal (35) and Luchsinger (36). Having ligated the aorta above the diaphragm, these authors injected such drugs as morphin, adrenalin and nicotin into the anterior vessels and were able to note the characteristic effects of these agents upon the intestine, splanchnic nerves, and pressure in the crural artery.

The present experiments, I believe, will leave no doubt as to the existence of this anastomosis, because they demonstrate in a quantitative way that the inferior cava still carries an appreciable quantity of blood after the ligation of the thoracic division of the aorta. This quantity of blood becomes increasingly larger as the level of compression is moved toward the diaphragm. This fact suggests that the intercostal arteries participate in this anastomosis. The succeeding protocol of experiment 14, embodied in table 6, has been selected to demonstrate these changes. They are more plastically revealed by figure 7 which reproduces the second of these tests. In these instances the aorta was compressed at a distance of about 5 cm. above the diaphragm.

Immediately upon the occlusion of this vessel the flow in the inferior cava decreased from 5.38 cc. in a second to 0.09 cc. in a second, while the caval pressure decreased from 1.6 mm. Hg to 0.8 mm. Hg. These values were retained throughout the period of aortic constriction. The carotid pressure, on the other hand, increased very decisively, namely, from 92.6 mm. Hg to 108.8 mm. Hg.

TABLE 6

The effects upon the blood flow in the inferior vena cava of the occlusion of the thoracic aorta

Experiment 14; cat: 4.4 kgm.; heart: 22 grams; frequency: 164 beats per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY OF BLOOD	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Carotid artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
1	3.6	19.8	5.60	92.6	1.6	Normal
2	3.5	19.8	5.66			
3	4.0	20.0	5.00			
4	3.8	20.0	5.26			
5	3.7	20.0	5.40			
Average.....			5.38	92.6	1.6	
6	20.6	2.0	0.09	108.8	1.0	Compression of thoracic aorta
7	5.0	18.0	3.60	8.09	1.2	
8	4.0	20.0	5.00	75.0	1.6	Normal
9	4.5	20.0	4.44	76.0		
10	7.4	20.0	2.70	88.5		Compression of thoracic aorta
11a	16.5	1.5	0.09	102.0	0.8	
11b	7.0	18.5	2.64	74.6	1.0	Normal
12	4.2	20.0	4.76		1.6	
13	4.0	20.0	5.00	85.0		
14	4.0	20.0	5.00	92.6		

8. *The blood flow in the superior vena cava during the occlusion of the thoracic aorta.* The changes in the blood stream of the superior vena cava during the compression of the thoracic aorta may readily be followed with the aid of table 7, representing a section of experiment 21. The values here given may be applied directly to figure 8. It will be seen that the circulation through the vessels of the head and forlegs may be

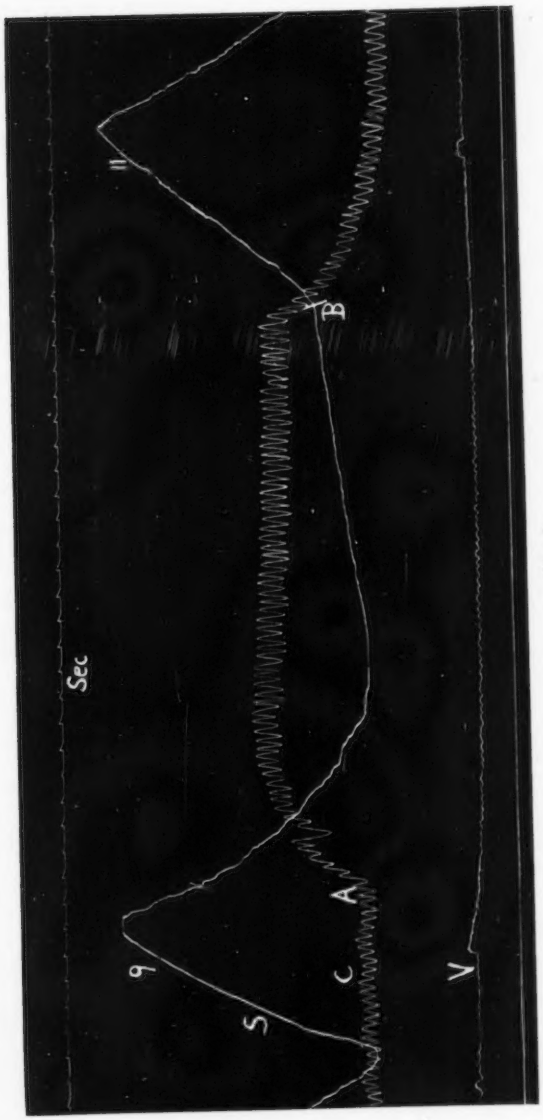

Fig. 7

very decisively increased by this means. In the example here given, the normal flow of 4.03 cc. in a second is contrasted against the maximal flow of 10.52 cc. in a second during the compression. Likewise, the pressure in the superior cava rose from 1.2 mm. Hg to 5.2 mm. Hg. Since the general blood pressure was ascertained in this case in the

TABLE 7

The effects upon the blood flow in the superior vena cava of the occlusion of the thoracic aorta

Experiment 21; cat: 4.6 kgm.; heart: 24 grams; frequency: 228 beats per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY OF BLOOD	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Femoral artery	Superior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
7	5.3	20.0	3.77	70.0	1.2	Normal
8	5.3	20.0	3.77			
9	5.0	19.8	3.96			
10	4.3	19.8	4.60			
11	4.2	20.0	4.76			
12	6.0	20.0	3.33			
Average.....			4.03	70.0	1.2	
13	4.2	20.0	4.76	28.0		Compression of thoracic aorta
14	3.8	20.0	5.26		2.5	
15	2.0	20.0	10.00		3.2	
16	3.2	20.0	6.25		5.2	
17	1.9	20.0	10.52	14.0		
18	3.7	20.0	5.40	68.0	2.5	
19	3.3	20.0	6.06	69.2	1.2	Normal
20	4.9	20.0	4.08			
21	4.3	20.0	4.64	74.6		
22	5.0	20.0	4.00			
23	5.2	20.0	3.84		1.5	
24	5.3	20.0	3.77	82.4		
25	5.0	20.0	4.00			

femoral artery, we note in the figure a decisive decline of this pressure toward zero.

The maximal flow obtained during the period of compression of the thoracic aorta amounted to 10.52 cc. in a second. The weight of this cat was 4.6 kgm. and that of its heart 24 grams. Under the experimental conditions here instituted, this value may be said to represent in an

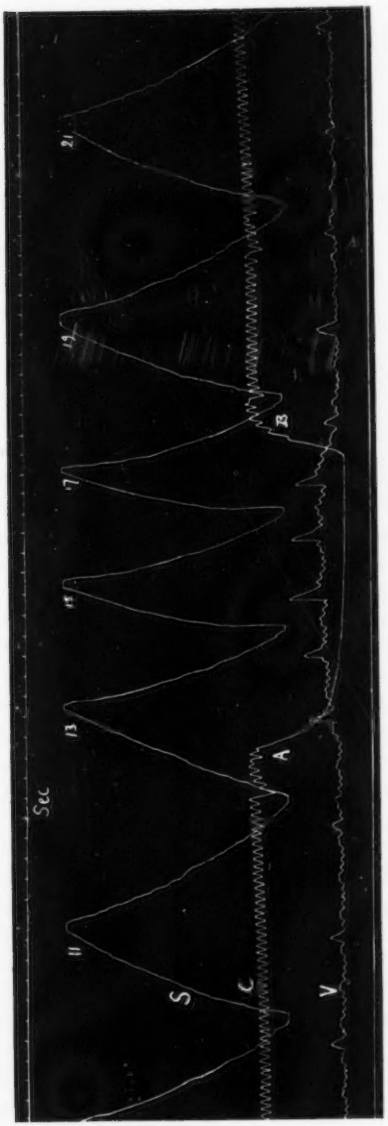

Fig. 8

approximate manner the second-volume of the systemic venous return as well as of that of the aortic blood stream. However, an allowance should be made for that relatively small portion of the total amount of blood which still finds its way by the anastomosing vessels into the posterior part of the body and is eventually returned by way of the inferior vena cava. This slight correction of 0.9 cc. having been made, the venous influx into the heart may be said to equal 11.42 cc. in a second. This value corresponds very closely to that previously established for the inferior vena cava during the period of compression of the vessels of head and forelegs. It yields a diastolic filling of the right auricle of 3.0 cc. for each beat of the heart, which appears to be a fair average value for a heart weighing close to 25 grams.

9. *The effects of stimulation of the greater splanchnic nerve and of the central end of the divided sciatic nerve.* In 1897 Biedl (37) observed that the stimulation of the splanchnic nerve produces a vasodilatation in the adrenal glands. A year later Dreyer (38) succeeded in proving the presence of vasoconstrictor fibers, and also showed that the excitation of the splanchnic nerve leads to a liberation of adrenin quite independently of the alterations in the vascularity of these glands. Burton-Opitz and Edwards (39) who calibrated the blood flow through the left adrenal body with the aid of a stromuhr, could not satisfactorily establish the presence of vasomotor fibers, because the rise in the arterial pressure following the stimulation of the splanchnic nerve, made it impossible for them to differentiate between a true vasomotor reaction and one possessing a mechanical basis. Thus, the increase in the blood flow through the adrenal bodies associated with the excitation of the splanchnic nerve, might be due either to a dilatation of these vessels or to the augmentation in the systemic blood pressure.

In the absence of definite data establishing the correctness of either of these possibilities, it might not be out of place to refer at this time to a number of observations which tend to emphasize the active character of this vascular reaction. Thus, it was noted that the blood flow did not always assume its previous value with the return of normal conditions of pressure, but remained augmented for some time after the stimulation. Furthermore, this increase in the blood flow resulted very promptly after the beginning of the excitation and rather in advance of the establishment of a high arterial pressure. It also seemed a significant coincidence that the excitation of the splanchnic nerve hinders the flow through the splanchnic organs, although it augments the venous drainage of the adrenal gland.

The changes pertaining to the portal and renal circuits have been described in detail by Burton-Opitz (40). They establish the fact that the vasoconstriction resulting in consequence of the stimulation of the splanchnic nerve, occasions an initial increase and subsequent decrease in the venous return from these organs (41). Contrariwise, it was noted that the flow through the hepatic artery is increased at this time, although it can readily be decreased by the excitation of the postganglionic fibers contained in the hepatic plexus (42). The observations of Edwards (43) upon the blood flow through the circuits of the carotid and femoral arteries, demonstrate that a change in the distribution of the arterial blood results very soon after the onset of the constriction of the splanchnic blood vessels. Clearly, therefore, the tendency is to counteract the initial effect of the splanchnic vasoconstriction by a shifting of the mass of blood in the peripheral vessels. This vascular compensation enables the heart to retain its venous supply in spite of the fact that the inflow from the hepatic and renal veins has been suddenly greatly reduced by vasoconstriction.

The observations of Johannson (44), proving that the rise in the arterial pressure occasioned by the excitation of the greater splanchnic nerve consists of two elevations, have been greatly amplified by the experiments of Elliott (45). The latter have shown that the second summit of the splanchnic rise in the arterial pressure is caused by a liberation of adrenin. This conclusion is based upon the fact that the removal of the adrenal glands destroys this elevation completely. Von Anrep (46) has confirmed these results and has succeeded in demonstrating that the general vasoconstriction upon which the second rise depends, is not destroyed by the denervation of organs supplied by the systemic arteries. It appears, therefore, that the rise in the general arterial pressure following the excitation of the greater splanchnic nerve is caused by three factors: namely, the direct constriction of the splanchnic blood vessels, the transfer of a superfluous amount of venous blood from these vessels into the general circuits of the body, and the later constriction of the general blood vessels by adrenin.

In amplification of these data it has been assumed by Ascher (47), Cannon (48), Elliot, von Anrep, Kahn (49), Jarisch (50) and others that the rate of liberation of adrenin is under the direct control of afferent impulses of all sorts. In accordance with the character of these impulses the liberation of this active agent is either increased or decreased. Thus, von Anrep states that the division of the nerves of the hind leg permits the blood vessels of this part to respond to afferent stimuli only if the adrenal glands have not been interfered with Ac-

cordingly, it is believed that the afferent excitation of nerves, such as the sciatic, evokes a reflex increase in the discharge of adrenin.

For reasons which need not be considered at this time, Stewart and Rogoff (51) claim that the stimulation of the sciatic nerve does not give rise to a greater formation of adrenin per unit of time, but is followed by a redistribution of the blood so that the denervated part becomes more vascular. This augmentation in its blood supply occasioned by the rise in the general arterial pressure, means that the amount of adrenin traversing the part in a given period of time is abruptly and markedly increased. Accordingly, it is possible to institute a vasoconstriction in a certain part by simply forcing a larger quantity of blood through it per unit of time without actually augmenting the output of adrenin by the glands themselves. In other words, the blood contains a certain minimal quantity of adrenin. By shifting the mass of the blood from one circuit into another, the parts so richly supplied are suddenly acted upon by increased amounts of adrenin. This explanation has been submitted in view of the fact that it was impossible to detect a difference in the adrenin output in samples of blood collected with and without the afferent excitation of nerves (52).

A second factor concerned in this redistribution of the blood following upon the stimulation of the central end of the sciatic nerve, is vasoconstriction, especially of the splanchnic area. It induces a retardation of the blood flow in the inferior vena cava. As a third factor are mentioned the changes in the depth and rate of respiration which are usually associated with the reception of sensory impressions. These alterations might affect the distribution of the blood rendering the contents of certain circuits rich in adrenin.

While my papers upon the changes in the blood supply of the different splanchnic organs have not been considered in this connection, I nevertheless venture to believe that they contain certain data which might well be made use of in testing the correctness of this assumption. The many records which I have published show that the first summit of the rise in blood pressure associated with the stimulation of the peripheral end of the splanchnic nerve, begins almost immediately upon the onset of the excitation. A series of experiments performed by me more recently in an attempt to ascertain the time relationship between the stimulation and the rise in pressure, have yielded the average value of 0.4 second. Certainly, the arterial pressure presents a decisive upward tendency before the expiration of 1.0 to 1.2 second. The briefness of this latent period clearly proves that the effect is localized. It is also obvious that the effector here at work is the smooth musculature of the

splanchnic vessels. The cause of its activation, however, is still unknown. We believe that the impulses generated at the seat of the stimulation give rise to a contraction of these muscle fibers either directly or in consequence of the liberation of some local metabolic agent. I make the latter modification in view of the work of Dale and Richards (53) pertaining to histamin.

It may be concluded, therefore, that the first summit finds its origin in the sudden partial exclusion from the circulation of the very vascular splanchnic organs. Burton-Opitz and Edwards have shown that this rise may be reproduced by the rapid occlusion of the arteries supplying these organs, and that the excitation of the splanchnic nerve then ceases to yield a first summit. A contention having as its basis a redistribution of the blood, cannot possibly explain these changes. As has been stated above, the adrenal glands do not participate in this vasoconstriction, but actually permit a larger amount of blood to traverse them.

Cannon employs this fact among others in endeavoring to disprove the contentions of Stewart and Rogoff, and rightly so, because even if the suprarenal flow possesses a relatively inconsiderable value in comparison with that of the inferior vena cava, any increase shown by the former can augment the adrenin content of the caval blood only if the flow in the cava remains the same. It will be shown later that the caval blood flow is not diminished and, hence, a greater concentration of adrenin by redistribution cannot take place. This result forces me to assume that the caval blood is able to retain its adrenin content only by augmenting the venous return from the lumbo-suprarenal vein, so that larger amounts of this agent actually reach this central vein. Whether a mere increase in the adrenal flow suffices to accomplish this end remains to be determined. It seems, however, that a simple flushing out of these glands cannot be sufficient. It actually requires a greater secretory activity on the part of the adrenal cells, in order to charge the larger amount of blood traversing these glands with normal amounts of adrenin. Obviously, the combination of a greater blood flow through the adrenals and retention of their former secretory activity can only lead to a diminished adrenin content of this blood. Thus, it has been shown by Burton-Opitz and Edwards that the venous discharge from the left adrenal body may be raised 40 to 60 per cent above normal by the excitation of the splanchnic nerve. In compensation this gland must augment its output of adrenin in an equal measure, at least. Stewart and Rogoff now assume that the stimulation of the splanchnic nerve occasions a considerable slackening of the blood flow in the inferior cava which enables this blood to become charged with normal amounts of adrenin. Inas-

much as the present experiments prove that such a retardation does not take place, the adrenin content of the caval blood cannot be determined by a simple redistribution of the blood.

It is admitted, of course, that vasoconstriction hinders the flow through the region of the constricted vessels, and that the arterial pressure rises whenever this area is sufficiently large to influence the general circulation. The calibrations of the arterial and venous supply of the liver (54) have shown that in a dog of medium size this organ receives about 7 cc. of blood in a second. This value must correspond to the inflow from the hepatic veins. Likewise, it has been demonstrated by these experiments that the excitation of the greater splanchnic nerve with a current of very moderate intensity diminishes this flow to about one-fourth of normal. It is easily conceivable that under ordinary circumstances this relatively abrupt loss of about three-fourths of the portal blood would lead to severe circulatory disturbances in the inferior cava and an abnormally small venous supply of the heart. These changes in the portal organs are augmented by similar decreases in the blood supply of the kidneys. Conservatively estimated, it may be said that a moderate constriction of the splanchnic vessels is able to reduce the second-volume of the caval blood stream by about 8 cc. While no data are at hand at present to allow us to estimate the total blood flow in the inferior cava in a dog weighing about 15 kilos, it may be assumed upon the basis of the present experiments performed upon cats that it is somewhat less that 15 cc. in a second. A reduction of this flow to about one-fourth of normal in consequence of the stimulation of the splanchnic nerve would seriously impair the action of the heart. Accordingly, it is noted that those channels which are not innervated by this nerve, permit the escape of a larger quantity of arterial blood in order to balance the diminished flow through the splanchnic vessels. This is the primary effect of splanchnic constriction. It is associated with a transfer of the superfluous quantity of venous blood from the splanchnic organs into the general circulation. Consequently, it cannot surprise us to find that the constriction of the splanchnic vessels is accompanied by an initial increase in the venous flow. A retardation in the blood flow of the inferior vena cava, such as might be employed to explain the constancy of the adrenin content of this blood in accordance with the redistribution hypotheses, does not result until the arterial pressure has reached its highest level. Besides, this retardation is clearly the result of a lessened cardiac discharge in consequence of a high peripheral resistance and not in consequence of a possible reduction of the inflow from the inferior vena cava.

I need not emphasize at this time the changes in the rate of the heart associated with the stimulation of the splanchnic nerve, because they possess no direct bearing upon this subject-matter. One statement of Stewart and Rogoff, however, seems to me to be misleading. It reads "We are not concerned here with compensatory reactions which may occur in other areas, leading, for example, as Edwards has shown, to increased flow in the superior cava." If compensatory changes in other regions are to be excluded, I fail to see how a redistribution of the blood can be effected. To my mind, such changes form the basis of the redistribution hypothesis.

Not entirely in harmony with the preceding statement is the following: "The observations of Edwards as to the compensatory increase of the blood flow through the head and limbs during stimulation of the splanchnic are not out of harmony with the supposition that stimulation of the central end of the sciatic may cause an increase in concentration of epinephrin in the blood of the inferior cava in the manner suggested without any change having occurred in the rate of liberation of epinephrin from the adrenals." Clearly, these experiments would be in distinct harmony with the redistribution hypothesis provided it could be shown that the excitation of the splanchnic nerve diminishes the blood flow in the inferior cava in a material degree, thereby allowing the retarded portion of blood to become thoroughly charged with adrenin secreted at a normal rate by the adrenals. The present calibrations of the flow in the inferior cava do not permit us to infer that such a retardation actually takes place. Indeed, the increased flow through the vessels not directly affected by the stimulation of the splanchnic nerve, makes such a loss of head and flow in the inferior cava unlikely. The primary result of this compensation is a certain constancy of flow in the cava, so that the heart may not suddenly find itself without an adequate supply of blood. Furthermore, it serves as a safety measure which prevents the arterial pressure from reaching an excessive height in consequence of splanchnic constriction.

Even if the flow in the inferior cava were reduced, establishing as a result of the constant inpouring of normal quantities of adrenin an increased concentration of this agent, it would be absolutely essential to transfer it in a reasonable length of time into the arterial channels. The value of the circulation-time between the adrenal veins and the arteries has been given by me as close to 6 seconds. This time applies to an etherized dog, weighing about 15 kgm. It may rightly be concluded that any considerable loss in pressure occasioned by the constriction of

the splanchnic vessels, would greatly prolong this time and cause a definite lateness of the second summit. The briefness of this latent period really speaks against the redistribution hypothesis and slow concentration of the adrenin.

The results of these calibrations of the blood flow in the central portion of the inferior cava during the stimulation of the left greater splanchnic nerve may be more closely followed with the help of table 8, representing the protocol of a part of experiment 9. It betrays in a fair manner the character of the changes obtained in the course of these tests. The normal second-volume amounted in this instance to 5.99 cc. About 3 seconds after the onset of the stimulation the flow increased to 7.14 cc. in a second, whereas about 8 seconds later it decreased to 5.50 cc. in a second. This moment corresponds in this case very closely to the beginning of the second summit of the rise in the arterial pressure. During this entire period the venous pressure showed definite fluctuations in agreement with the flow, but their amplitude did not exceed 1.0 mm. Hg. In addition to the initial phase of increased flow, these records reveal a phase of diminished flow coincident with the period of greatest arterial pressure.

This reduction in the venous supply and, hence, also in the ventricular output, finds its origin in a hindrance to the cardiac discharge occasioned by the high arterial resistance. It does not seem to be caused by a lessened venous supply. Further, the initial wave of slightly increased flow is explicable upon the basis that the constricting splanchnic vessels evoke a rapid transfer of a certain amount of their blood into the inferior cava. This conclusion is substantiated not only by the relationship in the time of this period of increased flow, but also by the fact that low degrees of arterial pressure tended to augment this increase and to diminish the subsequent retardation in the caval blood flow. The character of this increased flow is very similar to that noted by me while ascertaining the changes in the blood supply of the different portal organs during the excitation of the splanchnic nerve. It does not tend to uphold the suggestion of Stewart and Rogoff that the stimulation of the splanchnic nerve evokes an early retardation in the flow in the inferior vena cava and concentration of the adrenin.

The results obtained by the stimulation of the central end of the divided sciatic nerve are very similar to those just described. At no time have I observed an initial retardation in the caval flow, favoring the redistribution theory. A slight retardation sets in finally at a time when the arterial pressure has reached its maximal value. The latency

of this reaction, as well as its general character, has led me to believe that it is due to a lessened ventricular discharge in consequence of the high peripheral resistance.

TABLE 8

The changes in the blood flow in the inferior vena cava evoked by the stimulation of the greater splanchnic nerve

Experiment 9; cat: 5.3 kgm.; heart: 23 grams; frequency: 182 beats per minute

PHASE OF STROMUHR NUMBER	TIME	TOTAL QUANTITY OF BLOOD	QUANTITY PER SECOND	BLOOD PRESSURE		PROCEDURE
				Carotid artery	Inferior vena cava	
	seconds	*cc.*	*cc.*	*mm.* Hg	*mm.* Hg	
7	3.8	20.0	5.26	96.8	2.0	Normal
8	3.8	20.0	5.26			
9	3.0	20.0	5.71			
10	2.9	20.0	6.89			
11	3.0	20.0	6.66			
12	3.2	19.8	6.18			
13	3.5	19.8	5.65			
14	3.1	20.0	6.38			
Average.....			5.99	96.8	2.0	
15	3.1	20.0	6.38	120.0	2.8	Stimulation left greater splanchnic nerve
16	2.8	20.0	7.14	121.5		
17	2.6	20.0	7.65	122.0		
18	3.6	19.8	5.50	125.6	1.5	
19	3.7	19.8	5.35	128.0		None
20	3.7	19.8	5.35			
21	3.8	19.8	5.21			
22	4.0	20.0	5.00			
23	3.8	20.0	5.26	120.0		
24	3.8	20.0	5.26			
25	3.6	20.0	5.55	110.5		
26	3.5	19.8	5.65			
27	3.2	19.8	6.18			
28	3.4	19.8	5.82	95.0		
29	3.0	19.8	6.60			
30	3.1	19.8	6.38	96.0	2.0	

Von Anrep states that the vasoconstriction in the denervated hind limb or kidney following the excitation of the central end of the divided sciatic nerve, is occasioned by a reflex increase in the liberation of

adrenin. This explanation is in agreement with the expositions of Cannon. Stewart and Rogoff, on the other hand, suggest that it is due to the fact that the larger amount of blood forced through the passive vessels brings their walls in contact with a greater amount of adrenin per unit of time. In other words, the vasoconstrictor reaction then ensuing does not find its origin in a greater liberation of adrenin, but in an increased blood supply of this part. Although each unit of blood retains its original content in adrenin the denervated area receives more adrenin for the reason that a larger quantity of blood passes through it.

In my experience I have never observed vasoconstrictor phenomena evoked by simply forcing a larger quantity of blood through a part, whether normal or denervated. The results of the experiments of Burton-Opitz and Lucas (55) show that the increased flow pursues a course parallel to the changes in the arterial blood pressure, and is, therefore, passive in its nature. In accordance with the suggestion of Stewart and Rogoff, the vasoconstriction might be expected to set in within a few seconds after the beginning of the inrush of arterial blood into the denervated part. At no time have I observed a retardation in the arterial supply at so early a time after the onset of the rise in the arterial pressure following the excitation of afferent nerves. Since the experiments of von Anrep refer the subsequent vasoconstriction to a late inrush of adrenin, this early increase in the blood supply of the denervated part may rightly be given a mechanical cause. It appears to be occasioned by the rise in the arterial pressure associated with the partial exclusion of the splanchnic organs from the circulation directly after the onset of the stimulation. Since the subsequent vasoconstriction diminishes the vascularity of this part, the time allowed for the redistribution of the blood would be very brief. In accordance with the determinations of the blood supply of the hindleg of a dog weighing about 15 kgm., it may be concluded that the second-volume of the blood stream of the femoral artery equals 0.85 cc. (56 and 57). Even if considerably increased by the denervation of this part, it does not seem likely that so small a quantity of blood could contain sufficient adrenin to produce vasoconstriction by redistribution in the course of 6 to 8 seconds. This time represents the latency between the beginning of the stimulation of the splanchnic nerve and the appearance of the second summit. The view of von Anrep which refers the final vasoconstriction to a reflex delivery of a greater amount of adrenin, does not meet with this objection.

10. *The volume and velocity of the blood flow in the venae cavae.* The forty-two experiments of this series have yielded certain data which enable us to calculate the normal blood flow as well as the velocity of the blood stream in the venae cavae. Tables 9 and 10 contain in addition to these values the weight of each animal, the weight of its heart, the inter-

TABLE 9

The volume and velocity of the blood flow in the inferior vena cava

EXPERIMENT NUMBER	WEIGHT OF		HEART FREQUENCY PER MINUTE	AVERAGE SECOND-VOLUME OF BLOOD FLOW OF INFERIOR VENA CAVA	BLOOD PRESSURE			DIAMETER OF VENA CAVA	VELOCITY
	Cat	Heart			Car. art.	Fem. art.	Inferior vena cava		
	kgm.	*grams*			*mm.* Hg	*mm.* Hg		*mm.*	*mm.*
4	4.1	27	180	4.04	106.4		1.0		
6	5.2	22	192	5.64	96.4		1.0	8.0	112.3
7	4.2	20	165	4.62	88.6		1.2	7.8	96.8
8	4.0	18	188	6.18	105.0		1.5	7.8	129.6
9	5.3	23	182	5.99	96.8		2.0	8.1	116.3
10	4.4	24	180	6.84	90.4		2.0		
12	4.6	22	172	6.39	91.0		1.0		
14	4.4	22	164	5.38	92.6		1.6	8.0	107.1
15	3.6	18	176	5.94	94.5		2.0		
17	4.5	22	175	5.64	98.7		1.2	8.0	112.3
18	5.8	25	184	7.02	102.0		1.5	8.2	133.2
19	4.7	21	172	5.28	94.7		1.5	8.0	105.1
20	4.0	20	195	4.67	94.0		1.5		
22	4.2	20	186	4.50	104.6		1.0		
23	3.8	18	200	5.28	95.0		1.2		
26	4.7	25	188	6.12	102.6		1.0	8.0	121.9
29	3.8	18	146	2.94		74.3	1.2		
30	5.2	25	154	3.98		110.7	2.0		
31	4.8	24	204	8.22	108.2		1.5	8.0	163.7
39	4.6	24	180	7.45	92.0		1.0	8.0	148.4
Average	4.5	22	179	5.60	97.3	92.5	1.4	7.9	122.4

nal diameter of the blood vessel, and the arterial and venous pressures. Only those animals have been included in these tables which have shown a substantial arterial pressure, so that an average pressure of about 100 mm. Hg could be obtained. The results of twenty-eight experiments closely approach this value. The first twenty of these deal with the dynamical conditions prevailing in the inferior vena cava

(table 9), and the last eight with those existing in the superior vena cava (table 10).

The compilation of the blood flow in the inferior vena cava (table 9) has yielded an average volume of 5.60 cc. in a second. A flow of this magnitude is present in a cat weighing 4.5 kgm. and possessing a heart weighing 22 grams. The arterial pressure of 97.3 mm. Hg approaches the standard value of 100 mm. Hg so closely that no corrections need be made. The venous pressure is 1.2 mm. Hg.

Table 10 which includes the calibrations of the blood flow in the superior vena cava, has given the average value of 4.02 cc. in a second in a cat weighing 4.3 kgm. and possessing a heart weighing 20 grams. The

TABLE 10

The volume and velocity of the blood flow in the superior vena cava

EXPERIMENT NUMBER	WEIGHT OF		FREQUENCY OF HEART PER MINUTE	AVERAGE SECOND VOLUME OF BLOOD-FLOW	BLOOD PRESSURE		DIAMETER OF VENA CAVA	VELOCITY PER SECOND
	Cat	Heart			Femoral artery	Superior vena cava		
	kgm.	*grams*			*mm.* Hg	*mm.* Hg	*mm.*	*mm.*
21	4.6	24	228	4.03	70.0	1.2	5.2	189.9
32	3.6	18	192	4.50	107.5	2.0		
34	4.0	20	172	3.75	96.1	1.0	5.0	191.4
35	4.2	20	182	3.80	94.6	1.2		
36	4.4	20	175	4.10	94.2	1.0		
37	5.0	21	180	3.96	90.4	1.0	5.5	130.9
38	4.0	18	204	3.42	89.4	1.0		
42	4.6	22	186	4.62	92.5	1.5		
Average	4.3	20	189	4.02	91.8	1.2	5.2	170.7

arterial pressure, as well as that prevailing in the cava, exhibits a height which may be directly compared with that previously noted in the inferior cava.

If the second-volume of the flow in the inferior cava is now compared with that in the superior cava, it will be noted that the latter accommodates less than three-fourths of the quantity of blood present in the former. This relationship appears to be the reverse of that noted before birth, because it is commonly stated that the vessels of the head receive a much larger quantity of blood than those of the posterior part of the body. This statement is not based upon actual quantitative determinations of the blood flow, but solely upon the character and

distribution of the blood vessels. The inference embodied in it is that the rapidly growing central nervous system requires a much larger quantity than the relatively passive organs of the abdomen. If this contention is correct, extra-uterine life reverses this relationship.

If the second-volume of the flow in the venae cavae is now compared with the frequency of the heart, it will be observed that the right auricle receives during each diastole 1.87 cc. blood from the inferior cava and 1.30 cc. from the superior cava, making a total of 3.17 cc. per beat. Leaving out of consideration the flow through the coronary system, this value must correspond to the volume of the aortic blood stream. The experiments previously cited in sections 6 and 8 of this monograph have given a diastolic filling of the heart of 2.1 cc. and 3.0 cc. respectively. The former value pertains to a heart weighing 18 grams, and the latter to one weighing 20 grams. The present average value of 3.17 cc. per beat may be applied to an organ of 22 grams. In general, therefore, it may be concluded that the heart of a cat of medium size (4.0 to 4.5 kgm.) receives about 3.0 cc. of caval blood during each diastole.

The average internal diameter of the inferior vena cava near the heart is 7.9 mm. The velocity of the blood stream in this portion of this vessel amounts to 122.4 mm. in a second. Likewise, the internal diameter of the superior vena cava is 5.2 mm., and the velocity of the blood stream 170.7 mm. in a second. These values pertain to a cat weighing about 4.5 kgm.

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STUDIES ON THE FRAGILITY OF THE RED BLOOD CELLS

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The phenomenon of hemolysis has been a matter of great interest to the physiologist. Hypotonic saline solution has been the agent which has been of greatest use in studies on the fragility of the erythrocytes. Normal human blood cells show a fairly definite point of beginning and complete hemolysis when placed in hypotonic salt solutions of diminishing strengths. The varying figures for normal blood which have been reported by different observers can probably be explained by differences in the technique used in performing this test. There are several substances which when added to blood in vitro are known to increase the fragility of the red blood cells in hypotonic saline. Other agents have just the opposite effect. These substances may act either on the lipoid or protein portion of the erythrocytes. Likewise in certain diseases the red cells show increased or decreased resistance to hemolysis in salt solution. In hemolytic family icterus there is a marked increase in fragility. In splenectomized animals the fragility is decreased. Although saline solution is an artificial means to use in testing the resisance of the red cells, it probably is as useful as any other substance. Pearce (1) and his co-workers have shown that the red corpuscles of splenectomized animals show an increased resistance not only to hypotonic saline, but also to saponin and cobra venom.

We have been interested in ascertaining the effect of certain substances on red cell fragility in saline solutions. In most instances the substances have been added to the blood in vitro. In certain experiments the red corpuscles have been allowed to remain in contact with the substance for a time and then washed free and tested for fragility. The effect of ether anesthesia and cyanosis on the fragility of the red corpuscles has been studied in vivo. An investigation along this line has revealed some interesting facts which seem of sufficient interest to report.

Technic. Our method of testing the fragility of the red blood cells has already been described (2), but it may be well to review briefly. Three cc. of blood are drawn with a dry Luer syringe and expelled into a centrifuge tube containing 3 cc. of an 0.85 per cent solution of sodium chloride and sodium citrate respectively. The tube is then centrifuged until 3 cc. of clear supernatant citrated plasma can be withdrawn and discarded. The blood cells and remaining citrated plasma are well mixed and 0.1 cc. of this citrated blood is added to each of a series of ten test tubes containing 1 cc. of saline solution, starting at 0.5 per cent and diminishing in gradations of 0.025 per cent to 0.275 per cent. After standing one hour the tubes are gently centrifuged and the point of beginning and complete hemolysis noted. In some of our experiments we have used washed red cells collected in the same manner and washed twice with 0.85 per cent saline.

Normals. Using this technique we have found the great majority of normal bloods to show beginning hemolysis at 0.425 per cent and complete hemolysis at 0.325 per cent A few normal cases have shown beginning hemolysis at 0.4 per cent, but this was the exception. The following is a protocol of a normal case.

J. G. (9-8-20)

0.500	No hemolysis
0.475	No hemolysis
0.450	No hemolysis
0.425	Trace hemolysis
0.400	Moderate hemolysis
0.375	Distinct hemolysis
0.350	Marked hemolysis
0.325	Complete hemolysis
0.300	Complete hemolysis
0.275	Complete hemolysis

Butler (3) has shown that the fragility of the red cells is the same when using untreated or citrated blood. This we have found to be true. In two cases of hemophilia with normal fragility our results with untreated blood and with blood collected in citrated saline solution were always the same. He has also shown that washed red cells show slightly less resistance whether citrated or not. Using washed red cells we have found hemolysis to begin usually at 0.45 per cent and to be complete at 0.35 per cent in normal cases. We have performed a few experiments to ascertain whether the concentration of the red cells had any effect on our method. We found that a 25 or 30 per cent suspension gave the same results as a 50 per cent suspension of red blood cells. We have observed no change in the fragility of the erythrocytes after the citrated blood remained in the ice box 19 hours. However, after standing 48

hours there was a slight increase in fragility, and at 96 hours a marked increase in fragility, the red cells hemolyzing in 0.5 per cent saline. Standing did not seem to affect the point of complete hemolysis.

Hypertonic Saline Solutions

20 per cent NaCl solution	Marked hemolysis
15 per cent NaCl solution	Moderate hemolysis
10 per cent NaCl solution	Trace of hemolysis
5 per cent NaCl solution	No hemolysis

The hemolysis of blood in hypertonic saline solutions is probably due to the marked change in osmotic pressure, the cells becoming dehydrated.

This is furthermore shown by the following experiment. One cubic centimeter of washed red cells was added to 5 cc. of 5 per cent saline and allowed to remain 5 minutes. The tube was centrifuged and the supernatant saline withdrawn. The cells were then washed twice with 0.85 per cent saline. Hemolysis began at 0.475 per cent and was complete at 0.35 per cent. Therefore, the immersing of red cells in 5 per cent saline slightly increases their fragility.

Repeating this experiment with 2.5 per cent saline, we found no change from the normal. The intravenous injection of saturated salt soluion, (35 per cent), has been recommended in cases of increased intracranial pressure (4). It is said to have no harmful effect on the red cells, as evidenced by no change in their fragility. This must be due to the fact that the hypertonic saline is diluted sufficiently in the blood stream.

Sodium bicarbonate solutions

6.0 per cent sodium bicarbonate solution	0
5.0 per cent sodium bicarbonate solution	0
4.0 per cent sodium bicarbonate solution	0
2.0 per cent sodium bicarbonate solution	0
1.0 per cent sodium bicarbonate solution	0
0.75 per cent sodium bicarbonate solution	0
0.50 per cent sodium bicarbonate solution	0
0.475 per cent sodium bicarbonate solution	Trace
0.450 per cent sodium bicarbonate solution	Trace
0.425 per cent sodium bicarbonate solution	Trace
0.40 per cent sodium bicarbonate solution	Moderate
0.375 per cent sodium bicarbonate solution	Marked
0.350 per cent sodium bicarbonate solution	Complete
0.325 per cent sodium bicarbonate solution	Complete
0.300 per cent sodium bicarbonate solution	Complete
0.275 per cent sodium bicarbonate solution	Complete

It is seen that the blood cells begin to hemolyze at 0.475 per cent sodium bicarbonate solution and show complete hemolysis at 0.35 per cent. The red blood cells show nearly the same fragility in sodium bicarbonate solutions as in saline.

An interesting effect of bicarbonate solutions on the fragility of the red cells was seen in the following experiment: One cubic centimeter of washed red cells was suspended in 6 per cent sodium bicarbonate solution for 10 minutes and then the bicarbonate was removed and the cells washed twice with 0.85 per cent saline. These bicarbonate-treated cells were found to have an increased resistance in saline solutions. The washed red cells untreated began to hemolyze at 0.45 per cent and were completely hemolyzed at 0.35 per cent. The bicarbonate treated cells began to hemolyze at 0.4 per cent and were not completely hemolyzed at 0.275 per cent. This experiment was confirmed several times with different bloods. No reason for this increased resistance is offered except that perhaps the bicarbonate content of the red cells is affected by this treatment and thus resistance increased. These results may have some bearing on the next experiments.

RED CELLS TREATED WITH 6 PER CENT SODIUM BICARBONATE		UNTREATED WASHED RED CELLS
No hemolysis	0.500	No hemolysis
No hemolysis	0.475	No hemolysis
No hemolysis	0.450	Trace hemolysis
No hemolysis	0.425	Moderate hemolysis
Trace hemolysis	0.400	Marked hemolysis
Moderate hemolysis	0.375	Marked hemolysis
Moderate hemolysis	0.350	Complete hemolysis
Marked hemolysis	0.325	Complete hemolysis
Marked hemolysis	0.300	Complete hemolysis
Marked hemolysis	0.275	Complete hemolysis

Effect of CO_2 gas. Butler has shown that CO_2 gas markedly decreases the resistance of the red blood cells. We have confirmed this observation. CO_2 gas was bubbled through the citrated blood for 1 minute. The cells showed beginning hemolysis at 0.5 per cent and complete hemolysis at 0.4 per cent as contrasted with readings of 0.425 per cent and 0.325 per cent in normal blood.

Van Slyke and Cullen (5) have shown that when CO_2 gas is passed through blood there is an increase in the bicarbonate content of the plasma and a decrease in the chloride content. This procedure also

causes a decrease in Na and K-ions in the red cells and an increase in the chloride content. In other words, CO_2 gas passed through blood causes an increased acidity of the corpuscles.

This increase in the acid content of the corpuscles probably accounts for their increased fragility as acids have marked hemolytic power. Butler has also shown that when oxygen is bubbled through the blood, the resistance of the red corpuscles is increased. Van Slyke and Cullen show that this procedure decreases the bicarbonate content of the plasma and increases the chloride content. At the same time the alkaline content of the corpuscles is increased. This probably accounts for the increased resistance of the corpuscles and also for the increased resistance found by us in the previous experiment when the red cells were immersed in bicarbonate solution before testing their fragility. It makes a difference in the fragility test whether arterial or venous blood is used. Smith, Means and Woodwell (6) have recently shown that the corpuscles gain over 7 per cent by volume of CO_2 when passing from artery to vein, therefore the corpuscles of the venous blood would be less resistant than those of the arterial blood. This explains why the results with our technic showed the corpuscles to have less resistance to saline than with Butler's method. In his method arterial blood is used, with ours, venous blood.

Cyanosis. We have tested the fragility of the red corpuscles in three patients with cardiac disease and cyanosis. All showed increased fragility. The most striking results were obtained in two patients with congenital heart lesions and marked polycythemia. The results of one test are given below.

NORMAL		CONGENITAL HEART DISEASE WITH CYANOSIS
No hemolysis	0.500	No hemolysis
No hemolysis	0.475	Trace hemolysis
No hemolysis	0.450	Moderate hemolysis
Trace hemolysis	0.425	Marked hemolysis
Moderate hemolysis	0.400	Marked hemolysis
Marked hemolysis	0.375	Complete hemolysis
Marked hemolysis	0.350	Complete hemolysis
Complete hemolysis	0.300	Complete hemolysis
Complete hemolysis	0.275	Complete hemolysis

CO gas. Rous (7) found no change in the fragility of the red corpuscles in cases of poisoning from carbon monoxid gas. We have

confirmed this by experiments in vitro. CO gas bubbled through citrated blood and washed corpuscles in saline for varying lengths of time did not affect the fragility of the red cells to saline.

Arsenic. Gunn and Felton (8) have shown the marked effect of arsenious acid in increasing the resistance of the erythrocytes. Hill(9) has confirmed this in experiments with neoarsephenamine and Fowler's solution. Striking results may be shown in vitro with arsenic in the form of Fowler's solution. The following is one of our experiments:

One cubic centimeter of washed red cells was suspended in a mixture of 3 cc. of 0. 85 per cent saline plus 1 cc. of Fowler's solution and allowed to remain for 15 minutes. The red cells were then washed free from Fowler's solution by three changes of 0.85 per cent saline and then tested for fragility.

RED CELLS TREATED WITH FOWLER'S SOLUTION		UNTREATED WASHED RED CELLS
No hemolysis	0.500	No hemolysis
No hemolysis	0.475	No hemolysis
No hemolysis	0.450	Trace hemolysis
No hemolysis	0.425	Moderate hemolysis
No hemolysis	0.400	Marked hemolysis
No hemolysis	0.375	Marked hemolysis
No hemolysis	0.350	Complete hemolysis
No hemolysis	0.325	Complete hemolysis
Trace hemolysis	0.300	Complete hemolysis
Moderate hemolysis	0.275	Complete hemolysis

The cause of the marked resistance of the red cells after treatment with arsenic (Fowler's solution) is not clear. It may be due to a chemical action of the arsenic on the lipoid membrane of the red corpuscles causing them to become more impermeable for water.

Adrenalin. Using a 1 to 1000 solution of adrenalin chloride (P.D. & Co.), we found no deviations from the normal fragility.

Atropine. No effect on red cell fragility was noticed when 0.8 mgm. of atropine was added to 2 cc. of citrated blood and then tested for fragility with saline.

Diphtheria and tetanus toxin. In the test tube no hemolytic effects were observed when large amounts of soluble toxin (1cc. of toxin to 3 cc. of blood) were added to the red blood cells.

We have also studied the fragility of the erythrocytes in cases of diphtheria (2) and found no striking changes.

Ether anesthesia. Since ether is a well-known hemolytic agent, it was believed that the study of the blood fragility before and after anesthesia would be of interest. We have tested this point in four surgical cases and found no marked change in fragility.

CASE	BEFORE	AFTER	REMARKS
I	0.400—0.325	0.425—0.325	Ether for 35 minutes
II	0.425—0.325	0.425—0.325	Ether for 1 hour
III	0.425—0.325	0.425—0.325	Ether for 30 minutes
IV	0.425—0.325	0.425—0.325	Ether for 40 minutes

CONCLUSIONS

1. The fragility of the red blood cells is increased after treating them with CO_2 gas, and hypertonic (5 per cent) saline solution.
2. The fragility of the red blood cells is decreased after treating them with sodium bicarbonate solution (6 per cent) and arsenic (Fowler's solution).
3. The fragility of the red blood cells is unchanged after treating them with CO gas, adrenalin, atropine, diphtheria and tetanus toxins.
4. No marked change in the fragility of the red blood cells was found after ether anesthesia.
5. The fragility of the red blood cells is increased in cases of cardiac disease with cyanosis.
6. The important changes in the plasma and corpuscles produced by CO_2 gas and oxygen (Van Slyke and Cullen) are correlated with the effect of these gases on the fragility of the red cells. Another factor (CO_2 content of the corpuscles) which affects the results of the fragility test is here pointed out.

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RESEARCHES ON THE CIRCULATION TIME AND ON THE INFLUENCES WHICH AFFECT IT

V. The Circulation Time of the Spleen, Kidney, Intestine, Heart (Coronary Circulation) and Retina, with Some Further Observations on the Time of the Lesser Circulation

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This constitutes the fifth paper of a series the first four papers of which were published in the Journal of Physiology (1), (2). The method of measuring the circulation time of the retina was demonstrated at a meeting of the American Physiological Society and a specimen experiment was published in the Proceedings (3). No observations on the spleen or heart, with the exception of a brief reference in a text-book (4), have been published before, and on the kidney and intestine only observations in the rabbit. This paper contains experiments on dogs, cats, rabbits and, in the case of the pulmonary circulation time, on one bullfrog. The electrical method (with galvanometer or telephone) and the pigment injection method (with methylene blue) were employed. Identical results are given by these methods. The majority (twenty) of the experiments were done in the Physiological Laboratory of the Harvard Medical School in 1894.

I take this opportunity of paying my tribute of gratitude and affection to the memory of the late Dr. Henry P. Bowditch, who encouraged and aided my work in every possible way.

The circulation time of the spleen. This, like the circulation time of the kidney and intestine, is very susceptible to certain experimental conditions, being markedly lengthened by exposure and cooling of the organ. It is apt to vary much more in different experiments than the time from the jugular vein to the carotid artery (mainly pulmonary circulation time). The variations depend chiefly upon local changes,

as shown by the fact that they may be quite marked, while the time of the lesser circulation, or the time from the left ventricle to the origin of the splenic or renal artery may have remained constant, or only altered slightly. Vasomotor changes no doubt play an important part in altering the circulation time of these abdominal viscera under experimental conditions. But stagnation of the blood, however produced, whether associated with loss of water and increase in the relative proportion of corpuscles in shock conditions or not, would also cause lengthening of the circulation time.

In a dog, weighing 13.3 kgm., the circulation time of the spleen (mean of 20 observations) was 11.0 seconds. The spleen had been exposed for some time and had cooled considerably. The animal had been used previously for another experiment. The local application of warmth to the organ caused some decrease in the average circulation time (from 1 to 2 seconds). The protocol of the experiment was given in another paper (5).

In a dog weighing 6.48 kgm., anesthetised with morphine and chloral hydrate (intravenously), salt solution was injected into the central end of the left carotid artery. The splenic artery and vein were placed on the electrodes (unpolarizable). The arrival of the salt at artery and vein was detected by two distinct deflections of the galvanometer. Time to splenic vein: 9.0, 8.5 (underestimated), 8.8, 10.2, 9.0 (underestimated), 10, 2 (good), 11.2 seconds (overestimated). Time to splenic artery 3.5, 2.5, 3.3 seconds. Time to splenic vein again estimated: 9.7, 10.0 seconds; with the vein alone on the electrodes, 9.4 seconds. Average of 10 observations of time from carotid to splenic vein, 9.6 seconds; average of 3 observations from carotid to splenic artery, 3.1 seconds. Circulation time of spleen 6.5 seconds. Weight of spleen 16.8 grams. Distance from cannula in carotid to electrodes 25 cm. Average velocity of blood between origin of carotid and splenic artery not more than 70 mm. per second. Distance of spleen from electrodes, 4 cm. Not less than one second must be deducted from the circulation time of the spleen given above, for the time from the electrodes to the organ and back again, leaving the net circulation time of the spleen not more than 5.5 seconds.

In another dog, weighing 21.1 kgm., methylene blue (0.4 per cent in salt solution) was injected into a branch of the splenic artery toward the main artery. The time to a tributary of the splenic vein close to the spleen was 4 and 4.2 seconds in two observations. The observations were made soon after the abdomen was opened. The animal was in good condition, the spleen warm and the blood in the splenic vein ruddy. The amount of solution injected was 1.5 cc. in each observation. It is possible that with injection so near the organ, the pressure of the injection might have caused some diminution in the circulation time. Yet as the splenic artery was open toward the abdominal aorta, it is unlikely that much effect would be produced. The time from the jugular to the carotid was 9.6 seconds (average of 7 observations made with the galvometer, 7 cc. of 4 per cent sodium chloride solution being injected in each observation). Weight of spleen, 28.7 grams.

In cats the same variability in the circulation time of the spleen, depending presumably upon local conditions in the organ, were observed as in dogs. Two typical protocols follow.

Cat (female), 2.445 kgm. (chloral hydrate 1 gm. *per rectum*). Splenic artery and vein on electrodes. Injection of salt solution through cannula in central end of left carotid. Time to splenic vein: 10.3, 11.4, 11.4, 12.0 (somewhat overestimated), 11.4, 11.6 seconds. Average of 6 observations, 11.2 seconds. Time from carotid to splenic artery, 1.4, 1.2, 1.5, 1.2 seconds (average 1.3 seconds). Circulation time of spleen 9.9 seconds, or, allowing half a second for the time from the electrodes to the spleen and back again, the net time for the spleen would be 9.4 seconds. Distance from cannula in carotid to heart, 7 cm.; from heart to origin of coeliac axis, 11 cm. The splenic artery came off from the coeliac axis. Distance from spleen to electrodes on splenic artery 2 cm. Mean velocity of the blood from origin of carotid to splenic artery 110 mm. per second. Weight of spleen 3.5 grams.

With injection of salt solution into a cannula in the left jugular vein, and electrodes on the right carotid, the following values were obtained for the (uncorrected) time of the lesser circulation: 5.4, 5.4, 4.8, 5.4, 4.3, 5.8, 4.5 seconds (average 5.1 seconds). Distance of electrodes from heart, 8 cm. Even at the average speed from carotid to splenic artery, the correction for the time from left ventricle to the electrodes would only be 0.7 second. If 0.4 second be added for lost time between the cannula in the jugular and the right ventricle, the net time from right ventricle to aorta would be 4 seconds. The respiration was slow, only 12 per minute.

In this experiment no undue exposure of the spleen had occurred and it is not noted that the animal had cooled (the cats and rabbits were completely enclosed in a box containing hot water). Nevertheless the circulation time of the organ was more than twice that of the lesser circulation. In the next experiment the condition is illustrated in which the circulation time of the spleen was short, corresponding plainly to the excellent circulation in the organ.

Cat, 2.98 kgm. Deeply anesthetized with chloral hydrate (2 gm. throughout the experiment). Observations on the circulation time of the spleen were made as soon as the animal was under the anesthetic. The organ was warm and bright red. The blood in the splenic vein seemed about as red as that in the artery. Injected salt solution through cannula in central end of carotid. Time to splenic artery 2.0, 2.2, 1.6 seconds (average 1.9 seconds). The average velocity of the blood over the path from aorta to splenic artery could not have been quite 100 mm. per second. Time from carotid to splenic vein 5.8, 5.8, 5.6 seconds (average 5.7 seconds). Circulation time of the spleen 3.8 seconds. The organ after death was congested and weighed 12.0 grams.

The circulation time of the kidney. A fair number of observations on the renal circulation time in rabbits were published in the first paper (1), all showing a relatively long time, which was markedly increased by cold and diminished by warmth. Essentially the results in this respect are similar to those in the spleen. Another experiment may be cited, in which the temperature of the abdominal organs was well maintained.

Rabbit. 2.16 kgm. Chloral hydrate. Methylene blue (0.2 per cent in saline) injected into cardiac end of left external jugular. Color observed in left renal artery and vein. Time from renal artery to renal vein 6.8, 6.8, 6.4, 5.4, 6.4, 5.4 and 6.0 seconds, at 4:30, 4:32, 4:34, 4:41, 4:45, 4:48 and 4:51 p.m. respectively. Average circulation time of kidney, 6.2 seconds. The animal was in a warm box saturated with watery vapor. Rectal temperature was above 38°C. throughout the experiment. The kidney was not interfered with at all, only a little areolar tissue and fat being separated from the renal vein.

In another rabbit of practically the same size, also anesthetised with chloral hydrate, the time from renal artery to renal vein was somewhat longer (average of a number of observations 8.2 seconds). In both experiments the renal time was much longer than the pulmonary circulation time (two to three times as long).

In a dog weighing 13.3 kgm., the average net circulation time of the kidney was approximately 13 seconds, the net time of the lesser circulation (right ventricle to aorta) 6 seconds. But the kidney had been exposed and had cooled.

The circulation time of the intestine (and stomach). In a bitch weighing 3.2 kgm., salt solution was injected into the central end of the left carotid. Electrodes on a vein in the mesentery coming from the small intestine (galvanometer). Time to intestinal vein: 5.2, 5.8 and 5.7 seconds in three observations (average 5.6 seconds). Average time to the corresponding small intestinal artery, 2.9 seconds. Circulation time through intestinal wall, 2.7 seconds. The time from jugular to carotid was 6.2, 6.2, 6.0, 8.2 and 5.4 (average 6.4) seconds. The net time of the lesser circulation was reckoned at 4 seconds, considerably more than the intestinal circulation time. In larger dogs the disproportion would be still greater. In rabbits, as stated in the previous paper (1), the circulation time through a loop of intestine is usually not much different from the pulmonary circulation time. This presupposes that the intestines have not been allowed to cool and have not been much manipulated. Whether the circulation time of the intestines varies according to the phase of digestion has not been in-

vestigated. The short circulation time is obviously correlated with the shortness of the vascular circuit, arranged mainly transversely to the tube. This, of course, favors the passage of a relatively large quantity of blood through the intestinal walls per unit of time, no doubt a matter of importance in digestion and absorption from the tube. As very few observations on the circulation time of the intestines were given in the previous paper, some more will be cited here.

Rabbit, 1.442 kgm. Chloral hydrate (0.5 gm. *per rectum* and 0.2 gm. into the carotid). Methylene blue (0.2 per cent in 0.5 per cent sodium chloride solution) injected through a cannula in the central end of the left carotid. Observed a small artery and vein in the mesentery close to the large intestine. The pigment reached the artery almost at once. The difference in time of arrival at the artery and vein was 3.8 and 4.0 (average 3.9) seconds. The net circulation time of the intestine would be very little less than this. When the intestines were now exposed for a little time, it was easy to demonstrate a great showing of the circulation in the observed loop. The pigment could be seen merely creeping along the small arteries without getting into the veins at all. As already pointed out, these observations have a bearing on the production of shock by exposure and manipulation of the intestines.

Rabbit, 1.58 kgm. Chloral hydrate. Methylene blue solution injected through cannula in central end of carotid, and observed in the mesentery. Time between a small artery and the accompanying vein in the mesentery near the small intestine, 3.5 seconds. The time record was started as soon as the pigment reached the artery, and stopped when it reached the vein. Then observations were made of the time from carotid to the small artery and from carotid to the vein separately. Time from carotid to intestinal artery, 2.9 seconds; from carotid to the vein, 6.5 seconds. Difference, representing the circulation time of the intestine, 3.6 seconds, agreeing exactly with the previous estimation.

After this portion of the intestine had been exposed for some time it was observed that the circulation time was much lengthened. This affected both the time from carotid to the small intestinal artery and the time from carotid to the intestinal vein. Thus, in one observation the time from the carotid to the intestinal artery was 7.8 seconds, more than $2\frac{1}{2}$ times greater than before. When a small artery of a fresh piece of intestine, not hitherto exposed, was observed, the time to it from the carotid was 2.9 seconds, the same as to the other artery before exposure. It can be assumed that the mean velocity of the blood from the arch of the aorta, at least up to the origin of the superior mesenteric artery, had not been altered. Practically the whole delay in the path from the carotid to the small artery of the first loop must have been in the short arterial path in the mesen-

tery. The vascular block in the exposed intestine was therefore extreme.

In one experiment the circulation time in the two curvatures of the stomach was observed.

Rabbit, 1.98 kgm. Chloral hydrate (1.3 gm. *per rectum*). Curara. Artificial respiration. Injection of methylene blue solution into central end of right carotid. Time from gastric arteries on the lesser curvature to the corresponding veins, 6.4 seconds. In another observation the time from injection into the carotid to appearance of the pigment in the gastric veins on the lesser curvature was 7.2 seconds. In another set of observations the time from the smaller gastric arteries on the greater curvature to the corresponding veins was 5.0, 5.8 (rather overestimated), 5.2 and 5.4 seconds (average 5.4 seconds). The time from beginning of injection into the carotid to arrival of the pigment at the small gastric arteries on the greater curvature was 2.6 seconds. The time from injection to appearance of the pigment in a coronary vein was 4.8 seconds. The coronary circulation time at this part of the experiment was longer than usual, as will be seen in a later section of the paper.

In another rabbit, weighing 2.0 kgm. and anesthetised with chloral hydrate, salt solution was injected into the central end of the right jugular vein. The time to a branch of the superior mesenteric artery was 5.7 seconds. Of this time less than half was consumed in the lesser circulation. For the time from jugular to left carotid was 2.5 seconds (mean of two practically identical estimations).

In another rabbit weighing 1.95 kgm., anesthetised with chloral hydrate, injection was made into the central end of the left carotid artery, and the time to a small vein in the mesentery close to the small intestine in 3 observations was 6.6, 5.8 and 6.0 (average 6.1) seconds. This is the sum of the circulation time of the intestine and the time from carotid to the small intestinal artery.

The circulation time of the testis. Rabbit, 2.5 kgm. Chloral hydrate *per rectum* (1.2 gm. in 3 portions throughout the experiment). Injected 5 per cent salt solution into the cardiac end of the right external jugular, 0.4 cc. for each injection. Time to left carotid 2.8, 3.0, 2.8 seconds. Injected 0.6 cc. of the salt solution at each observation: time to carotid 2.6, 2.4, 2.5 seconds. Injected 0.4 cc. of the solution: time to carotid 2.4, 2.4, seconds. Average of all observations, (uncorrected) time of lesser circulation 2.6 seconds.

Time from jugular to arteries of spermatic cord: 5.4, 5.2, 5.0, 4.8 (average 5.1) seconds; from jugular to spermatic veins in the cord 9.2 seconds. Circulation time of testes 4.1 seconds, which should be reduced slightly for the time necessary for the blood to pass from the point of application of the electrodes to the testes and back again.

The testes were now exposed and felt cold. The time from jugular to spermatic vein in the cord (the vein was now isolated and placed on the electrodes) was 11.0 and 11.6 seconds in two observations, the (uncorrected) circulation time of the testes being increased to 6.2 seconds (vasoconstriction).

In a dog weighing 13.3 kgm. the circulation time of 7 seconds was observed for the testes. The great length of the narrow spermatic arteries and veins must be associated with a smaller slope of pressure between arteries and veins in these than in most organs. But in the organ itself the circulation does not appear to be a specially difficult one since the circulation time is not exceptionally long when cooling is avoided.

The coronary circulation time. All the observations were made with injection of methylene blue. The animals were anesthetised with chloral hydrate. The chest was opened and artifical respiration maintained. A typical protocol follows.

Rabbit, 1.765 kgm. Chloral hydrate (0.5 gm. *per rectum*). Curara subcutaneously. Methylene blue (0.15 per cent in saline) injected into the central end of the left carotid low in the neck. Time to a coronary vein: 2.6, 2.8, 3.2, 2.6, 3.6, and 3.0 (average 3.0) seconds. This represents the coronary circulation time, as there was no measurable interval between injection and arrival of the pigment at the origin of the aorta. The amount of solution injected was 2.5 cc. in each observation. The above estimations were made within a period of 40 minutes: at 2:15, 2:20, 2:30, 2:36, 2:38, 2:50 and 2:55 p.m. respectively. Two more observations, taken in the next 15 minutes (at 3:05 and 3:18 p.m.), gave 2.8 and 2.8 seconds.

With injection of the pigment into the cardiac end of the external jugular, the time to the carotid was now estimated at 3.4, 3.4, 3.2, 3.6 and 3.8 (average 3.5) seconds, at 3:42, 3:45, 3:46, 3:48 and 3:52 p.m. respectively. The amount of the solution injected varied from 2 to 3.5 cc. Distance of observed point on carotid from heart 5 cm., from cannula in jugular to heart 4 cm. The net time of the lesser circulation could not have exceeded 3 seconds; about the same as that of the coronary circulation.

In another rabbit weighing 1.4 kgm. the time to a coronary vein tributary, with injection of methylene blue into the central end of the right carotid, was the same, namely, 2.9 seconds. The arrival of the pigment at the origin of the aorta was seen to be practically instantaneous.

In some experiments the influence of stimulation of the peripheral end of the vagus on the coronary circulation time was studied. An example is given in the following protocol.

Rabbit, 1.72 kgm. Injected methylene blue (1.2 cc. of a 0.4 per cent solution in saline) into the central end of a carotid artery. Time to a coronary vein: 3.8, 3.8, 3.0 and 3.0 (average 3.4) seconds in successive observations from 11:55 a.m. to 12:08 p.m. Then injected 2.7 cc. of the methylene blue solution, and saw the pigment reach the coronary vein in 3.8 seconds.

Now observed a different coronary vein, as there seemed possibly to be some blocking of the one previously used. The time to the coronary vein was 2.6 and 2.4 seconds in two observations (at 12:27 and 12:33 p.m.) and 3.4 seconds in a

third (at 12:41 p.m.). Now ligated and cut one vagus, and observed the times 2.8 (at 12:49), 2.4 (at 12:57), and 2.4 seconds (at 12:59 p.m.).

During stimulation of the vagus, observed the arrival of the pigment at the coronary vein in 2.2 seconds (at 1:01 p.m.). Stimulation did not obviously affect the heart rate, although previously it had caused slowing. Put the electrodes on a fresh part of the vagus and again injected during stimulation. There was marked slowing of the heart. The time to the coronary vein was 2.8 seconds (at 1:12 p.m.), without stimulation 2.7 seconds (at 1:15 p.m.), during stimulation with the heart almost stopped, 3.0 seconds (1:17 p.m.); without stimulation 2.2 seconds (1:20 p.m.); during stimulation with considerable slowing, 2.0 seconds (at 1:22 p.m.). The heart was very rapid in the absence of vagus stimulation (234 beats a minute).

In this experiment it could not be seen that any definite effect on the coronary circulation time was caused by stimulation of the vagus. It must be noted that injection was made in each case soon after the beginning of vagus stimulation. It is difficult to see how in prolonged slowing of the heart with a fall of arterial pressure an increase in the coronary circulation time can be avoided, unless indeed the resistance in the path is diminished either by the relaxation of the myocardium or by vasodilatation. It is recognized that the conditions are much too complex for any simple observations on the coronary circulation time to throw light upon the question of the vasomotor innervation of the heart.

In other experiments observations on the coronary circulation time were combined with estimations of the amount of blood escaping from a wound in a coronary vein, during and without stimulation of the vagus. An example is given in the following protocol.

Rabbit, 2.05 kgm. Chloral hydrate (1 gm. *per rectum*). Injection of methylene blue solution into central end of the left carotid. The right carotid was connected with a manometer for registering the arterial pressure.

Time of the arrival of the pigment at a tributary of the coronary vein 4.2 and 4.2 seconds in two successive observations (at 4:20 and 4:25 p.m.). Time during stimulation of peripheral end of vagus (with marked fall of blood pressure and great slowing of the heart) 3.0 and 3.0 seconds in two observations (at 4:30 and 4:35 p.m.). Without vagus stimulation the time was now 4.4 seconds (at 5:05 p.m.). At 5:10 p.m. it was 4.4 seconds (without vagus stimulation) and at 5:15 p.m. only 2.6 seconds during stimulation of the nerve. There was no fall of blood pressure. At 5:23 p.m. the time was 2.6 seconds during vagus stimulation; at 5:40 p.m. 2.6 seconds without stimulation, and in two succeeding observations (without stimulation) 2.4 and 2.7 seconds. Artificial respiration was now stopped, and while the heart was beating feebly and slowly an injection was made during vagus stimulation. The time to the coronary vein was only 2.2 seconds.

In this and other experiments it was seen, by collecting the blood flowing from a cut in a large tributary of a coronary vein, that when the heart was completely stopped by stimulation of the vagus the outflow was diminished, but the diminution was not striking when it was merely slowed.

In a similar experiment on a dog weighing 6.55 kgm., it was observed that with each systole a gush of blood came from the cut vein, but little or none during diastole. The total solids in the blood collected in equal times in watch glasses or taken up with small sponges, during and without vagus stimulation, were compared in a series of observations. For example, in 15 seconds during strong stimulation of the vagus, by which the heart was greatly slowed and stopped for a little time, the solids weighed 0.153 gram; in 15 seconds without stimulation, 0.196 gram; in 15 seconds while the heart was slowed by weaker vagus stimulation, 0.071 gram; and in 15 seconds without stimulation, 0.80 gram. No anticoagulant was used, so that the outflow was generally diminishing rather rapidly.

In other observations the hemoglobin in the different specimens was estimated. Thus, the blood collected in 15 seconds with vagus stimulation contained a quantity of hemoglobin 10 per cent less than that collected immediately thereafter in 15 seconds without stimulation. In another pair of observations the total hemoglobin of the blood collected during vagus stimulation was 6 per cent less than that collected in the same time immediately thereafter without stimulation.

The circulation time of the retina. This was estimated by injecting a solution of methylene blue in physiological saline into the cardiac end of the external jugular vein in rabbits, and observing with the ophthalmoscope (indirect method) the arrival of the pigment at the central artery and vein. Probably by injecting into an ear vein, and providing for proper fixation of the animal's head, the time could be measured without anesthesia. But in all the experiments the rabbits were anesthetised with chloral hydrate. The protocol of a typical experiment follows.

Rabbit, 1.4 kgm. Chloral hydrate (0.5 gm. *per rectum*). Injected methylene blue solution into cardiac end of jugular vein. Time from central artery of the retina to central vein 1.8, 1.8, 1.8, 1.4 (underestimated), 2.0 seconds (overestimated). Average circulation time of retina 1.75 seconds. Time from jugular to central artery now 4.0 seconds; jugular to carotid artery low in the neck, 2.8 seconds. Further observations: time from jugular to retinal artery, 3.8 seconds (1:30 p.m.); retinal artery to retinal vein, 1.8 seconds (1:32 p.m.); and again 1.8 seconds at 1:37 p.m.; jugular to retinal artery, 4.0 seconds (1:42 p.m.); jugular to carotid, 2.3 seconds (at 1:46 p.m.), 2.5 seconds (1:50 p.m.).

Retinal artery to retinal vein at the center of the disc, 2.2 seconds (1:56 p.m.), and 2.4 seconds (rather overestimated) at 2:07 p.m.; again 2.4 seconds at 2:12 p.m. The *apparent* distance of the points of the retinal artery and vein observed in all the previous observations was nearly 20 mm. from the center of the disc.

The time from jugular to carotid was again estimated at 2.6 seconds (2:17 p.m.), and 2.6 seconds (2:19 p.m.). Time from jugular to central artery of the retina at the disc, 3.4 seconds (2.25 p.m.); and again, after giving ether, 3.6 seconds (2:38 p.m.).

In the first 6 estimations of the circulation time of the retina the average was 1.7 seconds, and in the 3 last estimations the average was 2.3 seconds. The path in the last set of observations was longer than in the first set, because in the last set it was from the center of the disc back to the center of the disc, whereas in the first set it was from a point on the artery about 5 mm. from the center back to a point on the vein at the same distance. This distance in these narrow vessels might easily consume several tenths of a second. For the average time from jugular to central artery was 3.8 seconds (mean of 5 observations), and from jugular to the observed point on the carotid 2.6 seconds (mean of 5 observations). The difference, 1.2 seconds, is the average time from the point on the carotid to the central artery (about 6 cm.). The average linear velocity along this path was 50 mm. a second, and it would of course be less in the retinal artery and still less in the retinal vein.

In another rabbit of the same weight and similarly anesthetised, the time from the jugular to the central artery of the retina was 4.0, 4.2, 4.2, 4.4, 4.2 and 4.2 (average 4.2) seconds, at 4:45, 4:47, 4:49, 4:51, 4:53 and 5:02 p.m. respectively. Time from jugular to a point on the carotid in the middle of the neck about 5 cm., from the central artery of the retina, 3.3 seconds at 5:28 p.m. and 3.2 seconds at 5:30 p.m. The time from this point on the carotid to the retina was therefore one second, and the average linear velocity of the blood over this arterial path about 50 mm. per second.

In another rabbit, weighing 2.15 kgm., anesthetised with chloral, the time from the jugular to the central artery of the retina was 5.2 and 5.4 seconds in two successive observations (average 5.3 seconds); from jugular to carotid in the middle of the neck, about 6 cm. from the retina, 4.2 seconds, leaving 1.1 second for the arterial path from the observed point on the carotid to the central artery of the retina. The mean linear velocity would accordingly be about 55 mm. per second. The retinal circulation time (from central artery to central vein) was 2.5 seconds (rather overestimated), 2.1 and 2.2. seconds in 3 observations, at 4:55, 5:00 and 5:05 p.m. respectively, just before the observations on the time from jugular to central artery and from jugular to carotid were made.

The results of the different estimations are seen to show a close agreement. The retinal vessels are so small and thin that with good illumination the arrival of the pigment is quite sharply seen. Such observations, as well as those given on the other vascular paths both in this and the previous papers, show clearly that the statement of Langlois and Desbouis (6) in their excellent papers on the influence of adrenalin and asphyxia upon the pulmonary circulation time, that it is not possible to make readings to less than at most half a second, is not correct. It is entirely a question of training and reaction time. Under proper conditions one does not need to hesitate for anything like half a second in order to determine whether a galvanometer deflection has begun or whether a blue tinge has appeared in a thin well-illuminated vessel, or whether the sound in the telephone with a properly balanced bridge has altered. I suspect that these writers may have confused the degree of concordance obtained in successive measurements of a given circulation time with the error due to hesitation of the observer. If that is what they mean, of course sometimes the different readings will vary much more than half a second and sometimes agree much more closely. That is a different matter altogether, the variation depending upon changes in the circulation, the respiration, the anesthesia, accidental movements of the animal, rate and amount of injection, etc. If they will time the beginning of some simple movement, color change or sound, produced and accurately timed independently of them, they will see, I think, that their error will be nothing like half a second. There can be little doubt that with platinum electrodes directly in contact with the blood, as employed by them, polarization must have been considerably more troublesome than in my observations, in which the vessels were not opened, and in which unpolarizable electrodes were employed when the galvanometer was used. The statement of Langlois and Desbouis, that when the vessel was sufficiently large my electrodes "en forme d'aiguille le traversaient" is evidently due to a misapprehension.

Now that pigments are frequently injected into a vein in man for determining the blood volume, it might sometimes be of interest to observe the time of passage of the pigment through the retina, if a suitable color could be employed. Possibly information of some value might be obtained in certain pathological conditions of the retina (or brain?). The time between the point of injection and the retinal arteries includes, of course, the pulmonary circulation time, which, with the quantity of blood in the lungs, determines the minute volume of the heart. To be

sure, the net pulmonary circulation time could not be got very accurately from the time of arrival of the pigment at the retina, if this could be clearly detected, since the correction for the venous path to the heart and the arterial path from the heart to the retina would be large, and impossible to make exactly. Yet for comparative purposes such observations, if feasible, might be of some use. A salt like sodium iodide, sometimes used in intravenous medication, could also be detected in samples of blood drawn off from an artery at known intervals of time after its injection into a vein, and the total time would also include, and perhaps to some extent measure, the pulmonary circulation time, although the distance of the radial artery from the heart being greater than that of the retinal arteries, the correction would be even heavier. While in most cases the estimation of the minute volume of the heart would be of greater value than the estimation of the pulmonary circulation time, the latter, so far as the uncorrected time is concerned, would be theoretically easier. I desire to point out distinctly that it is not suggested that such observations should be attempted in man, unless for other good reasons intravenous injections of suitable substances are in any case being made.

The time of the lesser circulation. In a previous paper (5) data have been given on 23 dogs. The (uncorrected) time from jugular, superior cava or right heart to carotid artery in 8 dogs ranged from 2.0 to 10.4 seconds, the net time from right ventricle to aorta from 1.7 to 8 seconds. The body weight of the 8 dogs varied from 1.0 kgm. to 21.1 kgm. In 15 dogs the (uncorrected) time from jugular, superior cava or right heart to the femoral artery varied from 6.4 to 17.2 seconds, the net time from right heart to aorta varied from 3 to 7 seconds. The body weights ranged from 4.9 to 32.2 kgm. The femoral artery was not chosen for the estimation of the time of the lesser circulation, as it is much too far from the heart. But it was being used in any case for observations on the minute volume of the heart, and the time from the left ventricle to the observed point on the femoral was directly measured in some of the animals. In these cases the net time from right heart to aorta was exactly determined. In other cases the data on the minute volume and the accurately estimated net time in other dogs of the same size permitted the net time to be estimated with, it is believed, only a small error. In a few of the animals the correction could only be made approximately from the measured distance. The gross times were, of course, what was actually measured, and are only affected by the ordinary errors of observation. The values given are the means of

a number of observations (as many as 11 or even more). In the smaller animals the gross times naturally differ less from the net times and require a smaller correction than in the larger animals. The lower in the neck the point of observation on the carotid is, the smaller, of course, is the correction. Additional results on a number of very small dogs follow.

Thus in a young puppy weighing 1.0 kgm., anesthetised with morphine and ACE, the time to the carotid with injection of methylene blue into the jugular was 2.0, 2.0, 2.0, 2.2, 1.8, 1.8 and 2.0 (average 2.0) seconds in 7 successive observations. The net time from right ventricle to aorta was reckoned at 1.7 seconds, the error being almost certainly not more than 0.1 second. In a young dog weighing 4.5 kgm., deeply anesthetised with morphine and some ACE mixture, the time from the jugular to the carotid in the middle of the neck was 5.6, 6.3 and 6.4 (average 6.1) seconds. The time from the jugular to the left renal artery was 6.4 and 6.4 seconds in two observations, practically the same as to the carotid, the measured distance along the two paths from the left ventricle being also about the same. The heart was slow (53 to 57 beats a minute), and with a slow heart the "lost time" in the heart, according to the point in the cardiac cycle at which the injected substance enters the ventricles, is greater, and the individual observations therefore more variable than with a rapid heart. The net time from right ventricle to aorta was reckoned at 4.5 seconds, but here there was probably room for an error of not much less than half a second.

In a puppy weighing 2.95 kgm., with injection of 0.4 per cent methylene blue solution into the external jugular vein, the time to the carotid was 3.8 and 4.0 (average 3.9) seconds in two observations. Later on, toward the end of the experiment, when the respiratory movements had become very rapid, the time increased somewhat, being 5.0 and 5.4 (average 5.2) seconds in 2 observations.

In a small adult dog weighing 2.6 kgm., anesthetised with morphine and curarized, injection of salt solution (2 cc. of 2.5 per cent solution) was made into a cannula in the right external jugular 8 mm. from the subclavian vein. The electrodes on the left carotid were 5.5 cm. from its origin. The following times to the carotid were observed: 3.3, 2.7, 3.3, 3.1, 2.8, 3.0, 3.2, 2.9, 3.0, 3.0 (average 3.0) seconds, at 1:55, 3:04, 3:07, 3:14, 3:16, 3:18, 4:53, 6:30, 8:05 and 8:07 p.m. respectively. The net time from right ventricle to aorta could not have differed much from 2.5 seconds.

In a young dog weighing 2.03 kgm., anesthetised with morphine and curarized, the injecting cannula was in the right external jugular 3.5 cm. from its junction with the subclavian. The time to a point on the carotid 8 cm. from its origin was 4.2, 4.1 and 3.9 (average 4.1) seconds.

In a dog weighing 3.7 kgm., the cannula in the jugular was 3 cm. from its junction with the subclavian. The time to the carotid, 5.5 cm. from the heart, was 4.8 and 4.7 seconds at 4:07 and 4:16 p.m. Two hours later, during which interval the cervical sympathetic had been stimulated many times, the circulation time from jugular to carotid was 3.7, 3.5, 3.5 and 3.3 in 4 observations extending over 20 minutes.

In a dog weighing 3.5 kgm., under morphine and curara, injection was made into the jugular 6 cm. from the heart. Time to right carotid, 5 cm. from the heart, 5.4, 5.3 seconds at 4:34 and 4:35 p.m. respectively with rectal temperature 39.1°C. Three hours later, the central end of the right vagus and the cephalic end of the right cervical sympathetic having been repeatedly stimulated in the interval, the time was 2.8 and 2.7 seconds, at 7:31 and 7:35 p.m. respectively. The temperature of the box in which the animal was contained had been considerably increased; the rectal temperature was now 40.1°C. and the pulse 211 per minute.

The data on these small dogs are given rather than those on the larger dogs, which have been sufficiently displayed in the previous paper (5), in order to afford a comparison with the times obtained on cats and rabbits not differing greatly in weight. It will be seen that the times from jugular to carotid are about the same in the cats as in dogs of roughly corresponding size.

Cat, 3.38 kgm. Chloral hydrate. Injection of methylene blue (0.2 per cent in 2.5 per cent salt solution) through cannula in right external jugular. The carotid was on electrodes, and the arrival of the solution was noted simultaneously by two observers from the change of color and the galvanometer deflections. The results were identical. The following times were obtained: 5.6, 6.2, 6.6, 6.2, 6.0, 6.2 (average 6.1) seconds. Distance of electrodes on carotid from heart, 9 cm. The net time from right ventricle to aorta was calculated at approximately 4.5 seconds.

A cannula was now put into the peripheral end of the carotid and a very small amount of methylene blue solution injected. The pigment reached the external jugular and posterior facial veins of the same side, at their junction, in 2.4 seconds, representing no doubt the time through short paths of muscle and skin. Now tied all branches of the common carotid except the superior laryngeal artery, and repeated the injection. The time to the junction of the external jugular and posterior facial veins was 3.4 seconds.

In another cat, weighing 2.35 kgm., anesthetised with chloral hydrate and occasionally a little ether, the time from jugular to carotid was 4.6, 4.2, 4.6, 5.0, 5.2, 5.6, 5.4 and 5.8 (average 5.0) seconds, at 3:15, 3:30, 4:00, 4:25, 4:27, 4:38, 4:43 and 4:50 p.m. respectively.

The results on a number of cats and rabbits are collected in table 1. In addition, the (uncorrected) time of the lesser circulation is often given incidentally in experiments on the circulation time by other paths, since it was looked upon, owing to its relative constancy and independence of experimental conditions, as a convenient standard of comparison. In cats 1 to 3 the time is from jugular vein to carotid artery, in cats 4 to 6 from left renal vein to carotid. There is no great difference in the distance of the point of injection from the heart in the two cases. The times given are the averages of a number of ob-

servations (6 to 9 in the majority of the experiments on cats, and 5 to 14 in the majority of the experiments on rabbits). In the rabbits the time was always from jugular to carotid.

One experiment on the pulmonary circulation time was made on a bullfrog. The animal was curarized. The cerebral hemispheres were destroyed. Methylene blue (0.2 per cent in 0.5 per cent sodium chloride solution) was injected through a hypodermic needle into the ventricle. The pressure in injecting was only enough to cause a few drops of the solution to enter the ventricle, without distending it. A lung was observed under the microscope by reflected light. The arrival of the pigment was very well seen. The circulation time to a middle-sized branch of the pulmonary artery was 3.2 seconds, to a similar pulmonary vein tributary 10.2, 10.2 and 12.0 (average 10.8) seconds. The net pulmonary circulation time was 7.6 seconds. It must be remembered that with a slow pulse

TABLE 1

NUMBER OF ANIMAL	WEIGHT	TIME TO CAROTID	NUMBER OF ANIMAL	WEIGHT	TIME TO CAROTID
	kgm.	*seconds*		*kgm.*	*seconds*
1	3.38	6.1	12	2.02	1.9
2	2.45	5.1	13	2.01	2.7
3	2.35	5.0	14	2.01	2.8
4		4.2	15	2.01	2.7
5		3.5	16	2.00	2.8
6		3.1	17	2.00	2.7
7	3.06	4.4	18	2.00	2.6
8	2.50	4.6	19	1.76	3.5
9	2.50	3.8	20	1.4	3.2
10	2.50	2.8	21	1.4	2.6
11	2.50	2.6			

The first 6 animals are cats, the rest rabbits. Cats 4, 5 and 6 weighed from 2 to 2.5 kgm.

the lost time in the heart, depending on the phase of the cardiac cycle at which the pigment enters the heart, may be considerable. On the average of a fairly large number of observations of the time to pulmonary artery and of the time to pulmonary vein any error due to this cause would not affect the difference between these times, that is, the pulmonary circulation time. With a pulse rate of 32 per minute (room temperature 21°C.), 4 heart beats would be required to displace the blood in the lungs. At lower temperatures in this poikilothermal animal the number of beats corresponding to one round of the pulmonary circulation would be still smaller. The pulse rate of a frog not nearly half grown but in which metamorphosis was complete, in the same tank and at the same time, was 58, and that of a bullfrog tadpole which had not yet undergone metamorphosis, 70 a minute.

In table 2 are shown the number of heart beats per minute corresponding to the net time of the lesser circulation (average of a number of observations in each case) in 19 dogs. When two pulse rates and circulation times are given under one animal, a marked change occurred in the course of the experiment either in heart rate or minute volume, accompanied or not by a change in the time of the lesser circulation.

TABLE 2

WEIGHT	PULSE RATE PER MINUTE	LESSER CIRCULATION		WEIGHT	PULSE RATE PER MINUTE	LESSER CIRCULATION	
		Time	Heart beats			Time	Heart beats
kgm.		*seconds*		*kgm.*		*seconds*	
32.2	97	8	13	11.7	75	5	6
	150	6	15	10.3	78	7.0	9
27.9	70	7	8	9.9	65	6	6.5
	140	7	16	9.8	80	7.5	10
21.1	160	7.5	20	9.8	57	7.5	7
18.2	68	8	9	7.2	50	5.0	4
17.5	75	6.0	7.5		55	5.0	4.5
15.2	68	7	8	6.5	83	4.5	6
12.8	135	4	9		100	3	5
12.3	63	6	6	4.9	88	4	6
11.8	100	6	10	4.5	60	4.5	4.5
	150	7.5	19	3.5	211	2.5	9

SUMMARY

The circulation time of the spleen was measured in a number of cats and dogs. When the organ was carefully protected from exposure and cooling, the time was generally of moderate length (4 to 5 seconds in round numbers, not more than the pulmonary circulation time, and in dogs sometimes less) but in one cat it was over 9 seconds, although it was not noted that any undue exposure had occurred. When the organ was purposely or accidentally exposed and cooled, the circulation time was markedly increased, to as much as 11 seconds (much more than the pulmonary circulation time, especially in cats). The suggestion is that these changes, to which the circulation times of the kidney and intestines are equally susceptible, are due to local vasoconstriction, aided perhaps, when shock conditions are induced by exposure of the abdominal viscera, by stagnation of the blood in the capillaries.

The circulation time of the kidney (in rabbits) even under the best conditions is relatively long (6 to 8 seconds), two or three times as long as the pulmonary circulation time. It is lengthened by exposure and

cooling. As long a time as 13 seconds was observed in a dog under these conditions. The local application of warmth can diminish the circulation time when it has been increased by exposure and cooling.

The circulation time of the intestines under good conditions is quite short (2.5 to less than 4 seconds), and not sensibly affected by the size of the animal. It is practically the same in dogs and rabbits. The short circulation time favors the passage of a large quantity of blood through the intestinal walls relatively to their actual content of blood. Exposure of a loop of intestine may greatly increase its circulation time, while the time of a neighboring loop which has not been exposed is as short as before. After rather long exposure and cooling, it was observed in some cases that pigment injected into the circulation entered the small intestinal arteries but never reached the veins, being blocked in the capillaries. Such observations have an obvious bearing on the mechanism of the production of shock by exposure and manipulation of the abdominal viscera. In one experiment the circulation time on the lesser and greater curvatures of the stomach was found to be 5 to 6 seconds, considerably longer than in the intestine, but it is not certain that the exposure of the stomach might not have been greater. However, the dimensions of the stomach and intestine are so different that a longer average time in the former would not be surprising.

The circulation time of the testis was observed to be somewhat less than 4 seconds in a rabbit (longer than the time of the lesser circulation). Cooling the organ increased the time to 6 seconds. In a dog the time was 7 seconds. These are approximately the net times through the organ. It would seem probable that the slope of pressure from the small arteries to the small veins is less than in most organs because of the resistance in the very long and narrow spermatic arteries and veins.

The coronary circulation time was estimated in rabbits and dogs. It is one of the shortest (2 to 3 seconds, in round numbers). This favors a large flow of blood through the heart muscle, relatively to the quantity contained at any time in the walls of the organ. No obvious effect was seen during stimulation of the vagus, unless the heart was completely stopped.

The circulation time of the retina is one of the shortest, if not the shortest measured in these experiments, being sometimes even less than 2 seconds (in rabbits). While it may be considered advantageous for the function of this membrane that its load of blood should be diminished as much as possible, a sufficient irrigation being nevertheless

ensured by the reduction of the circulation time, the dimensions of the structure and the minute distances to be traversed may be a sufficient explanation.

Previously published observations on the time of the lesser circulation are supplemented in certain respects. The time does not differ much in dogs and cats of about the same size. A table is given showing the number of heart beats corresponding to the time of the lesser circulation in dogs of different size. It varies, of course, greatly with the pulse rate and circulation time (from 4 to 20 beats).

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SECRETIN

V. Its Effect in Anemia, with a Note on the Supposed Similarity Between Secretin and Vitamin B

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In previous reports (1), (2), (3) we have shown that the subcutaneous injection of even small doses of secretin increases the erythrocyte count of rabbits. We were further able to demonstrate that this increase is due to direct stimulation by secretin of the hematopoietic activity of the bone marrow (3). Incidentally in the course of other experiments we have repeatedly observed that freshly received rabbits improved more rapidly (put on weight at a faster rate and developed a higher erythrocyte count) if they were receiving secretin injections than if they had the benefit of better dietary and hygienic conditions alone.

Abelous and Soula (4) claim that secretin brings about a superactivity of metabolism as shown by an increased elimination of nitrogen and mineral matter in the urine and an increase in the respiratory quotient together with a decrease in the glycogen content of the liver. In addition to stimulating the digestive secretions, pancreatic, biliary, intestinal, it causes, they say, the liberation of nutritive intracellular reserves to make way for the new reserves which constitute the products of digestion.

With these facts in mind it seemed not unlikely that the recovery of decidedly anemic animals might be hastened by the administration of secretin.

Fourteen full-grown rabbits, apparently normal and in good condition were put on a diet composed exclusively of broken polished rice after the making of initial red corpuscle counts. Further blood counts were made from time to time and the rice diet continued until the number of erythrocytes was reduced to about 4,000,000 per cubic millimeter

of blood. This required unequal periods of time, from 3 to 6 weeks, in the different rabbits so that each animal was considered individually in this respect. All the animls lost weight and after the first few days were exceedingly apathetic. Loss of appetite was a prominent symptom. It is perhaps worthy of note that the feces became gradually lighter in color, a fact which we take to mean a lessened biliary secretion. Lumiere (5) describes similar changes in pigeons fed on polished rice. He attributes the loss of appetite and the attendant starvation effects to lack of digestive secretions in turn due to the vitamin deficiency. He believes that the vitamins serve as stimuli to these secretions.

Four of the rabbits died from inanition before a very marked anemia had developed. Of the remaining ten four served as controls, the others will be referred to as the secretin group.

When a sufficient reduction in the number of the red corpuscles had been secured, each rabbit was put on a full diet (practically as much as it would eat) of oats, turnips, carrots and cabbage. They were weighed and corpuscle counts made at least every week. Those of the secretin group received daily, except Sunday, a subcutaneous injection of secretin, a dried acid extract (1) dissolved in physiological saline solution, 20 mgm. per kilogram of body weight. At the same time the controls were given a subcutaneous injection of an equal amount of physiological saline solution.

All the animals shortly began to increase in weight and gradual improvement in the erythrocyte count developed. At the same time the difference in the two groups was very striking. In figure 1 we have plotted the average number of erythrocytes per cubic millimeter of blood for the secretin group (solid line) and for the controls (dotted line), including the original count before the rice diet was started, the initial count at the time of changing from rice to full diet and the beginning of the injections and the average weekly counts from that time onward. In the secretin rabbits the count rises rapidly and is back to the original before the end of the 3rd week. It continues to rise steadily until at the end of the 8th week it is 27.30 per cent above the original. On the other hand in the group of controls the count rises hardly at all during the first 2 weeks, after that very gradually, and at the end of 8 weeks has scarcely attained the original level.

The weight curves (fig. 2) are practically parallel until the end of the 3rd week following the beginning of the injections. From then on the secretin rabbits put on weight more rapidly. At the end of 8 weeks

their average weight was 145 grams above the original while the weight of the controls averaged 108 grams below their original.

The anemic condition of our animals was undoubtedly due, indirectly at least, to a deficiency of the vitamin B. Voegtlin and Myers (6) as the result of their comparative observations conclude that there is a very direct similarity between secretin and vitamin B. Could, therefore, the marked improvement which we observed under the in-

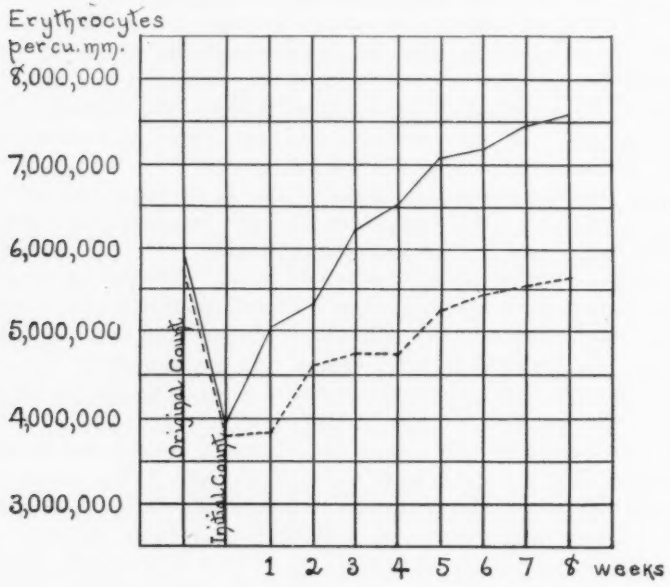

Fig. 1

fluence of secretin have been brought about by the addition of an equivalent excess of the water soluble vitamin? Vitamin most certainly stimulates metabolism. According to Lumiere (5) and Voegtlin and Myers (6) it also stimulates the production of the digestive secretions. Does it as well directly stimulate erythrocyte production?

Following the method described by Voegtlin and Myers (6) we prepared secretin from hog's intestine and vitamin B from brewer's yeast. One cubic centimeter of final preparation was equivalent

to 10 grams of intestinal mucosa or brewer's yeast respectively. Into each of five rabbits we injected subcutaneously 1 cc. of the secretin preparation per kilogram of body weight. The average of the erythrocyte counts before the injection was 6,088,000 per cu. mm. At the end of 1 hour after the injection the average count for the five rabbits was 7,156,000, an increase of 17.55 per cent. The second count was higher in every case, the maximal difference being 1,776,000 or 30.08 per cent, and the minimal difference 348,000 or 6.92 per cent.

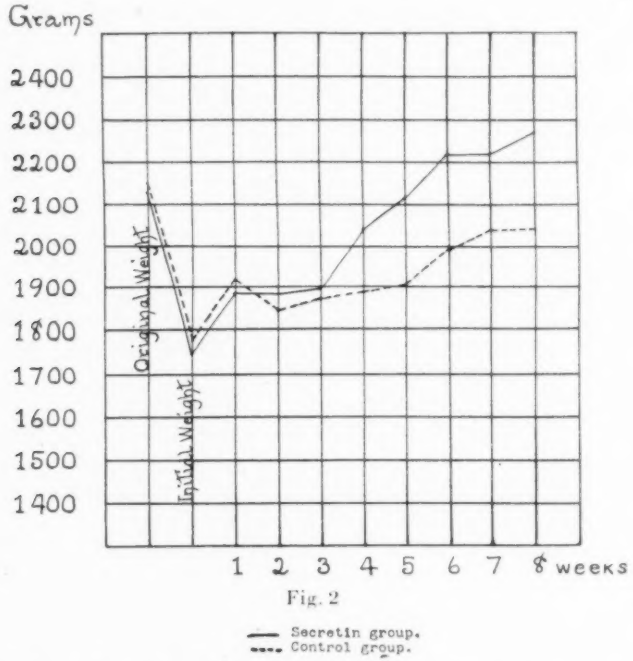

Fig. 2

Into each of five other rabbits 1 cc. of the vitamin preparation per kilogram of body weight was injected subcutaneously. The average initial count in these animals was 6,014,000 and at the end of an hour the counts averaged 5,990,000. In each case the second count was within 250,000 of the original. The number of red blood corpuscles in circulation was not increased by the administration of this vitamin preparation. Secretin and vitamin B, at least so far as effect on the blood cells is concerned, do not appear to be similar.

While these experiments were in progress Anrep and Drummond (7) reported the repetition of the experiments of Voegtlin and Myers. Their conclusion is that "the suggestion advanced by Voegtlin and Myers that vitamin B, or the anti-neuritic vitamin, is identical with secretin is not supported by experimental evidence."

CONCLUSIONS

1. The administration of secretin subcutaneously to anemic animals causes much more rapid improvement than can be obtained by dietary adjustment alone.

2. This improvement manifests itself by increased rate of blood regeneration and increased ability to put on weight.

3. Our results do not support the suggested similarity between secretin and vitamin B.

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ON THE ACTION OF CERTAIN SUBSTANCES ON OXYGEN CONSUMPTION

V. The Action of Potassium Cyanide in Relation to Respiratory Rate

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Although a large number of agents which are known to act upon living systems in widely different ways have been used by Child and other investigators in this laboratory to demonstrate the existence of axial susceptibility gradients in organisms and to modify development and regeneration on the basis of differential susceptibility, the substance which has been most extensively employed for this purpose is potassium cyanide. An extensive review and discussion of the literature dealing with the effects of cyanides upon physiological processes has recently been given by Hyman (1) in an earlier paper of this series, so that it is sufficient to state here that cyanides have been shown to be powerful inhibitors of oxidative processes both *in vitro* and *in vivo*. It has been shown by several workers in this laboratory that organisms or regions of organisms in which metabolic processes, and particularly those of oxidative nature, are going on rapidly are killed more quickly or inhibited more greatly in development by cyanide in concentrations above the limit of acclimation or tolerance than are those in which such processes are proceeding at a lower rate (for full references see Child (2)). Hence it might be expected that in order to produce such differential death or acclimation, potassium cyanide in a solution of given concentration, above the limit of acclimation, should lower the rate of oxidation to a greater extent in protoplasm of high oxidative activity than in protoplasm of the same species in which oxidation is going on at a lower rate.

The present investigation was therefore undertaken with the object of ascertaining whether exposure to a solution of potassium cyanide of suitable concentration for a given time and under identical conditions will actually produce a differential effect upon the rate of respiration

of parts of organisms of the same species which are similar in structure, but which show considerable differences in rate of respiratory exchange.

EXPERIMENTAL DATA

In an earlier paper (3) it has been shown that in two species of Pacific coast polychaetes, *Nereis virens* and *N. vexillosa*, and in the fresh water oligochaete, *Lumbriculus inconstans*, there exists along the major axis a double gradient in rate of oxygen consumption. This gradient is parallel to the susceptibility gradient described by Hyman (4) for several species of microdrilous oligochaetes, to the death gradient described for the polychaete *Ophryotrocha* by Czwiklitzer (5), and to the double gradient in electrical potential described by Morgan and Dimon (6) for the earthworm and more recently observed in several species of annelids by Hyman and Bellamy (unpublished). In *Nereis* and in *Lumbriculus*, pieces of sufficient length to render stimulation by section negligible, and taken a short distance posterior to the pharynx, show a considerably higher rate of oxygen consumption per unit weight than pieces of approximately the same length taken somewhat anterior to the middle of the body; and similar pieces from the posterior growing region show even a much higher rate of oxygen consumption than do the anterior pieces. It is quite evident then that the pieces just described fulfil all of the conditions required of material for the present investigation, for they are parts of organisms of the same species which are as nearly as possible identical in structure, and which show large differences in rate of respiration.

The experiments recorded in this paper were performed upon the same pieces of *Nereis vexillosa* as were those described in the paper just referred to. After the rate of respiration in sea water had been determined by the method which is fully described in the earlier paper (3), the bottles containing the pieces were filled with a freshly made solution of potassium cyanide in sea water, and the amount of oxygen consumed in a given time determined by the same method, the control bottle also being filled with a quantity of the same cyanide solution. The concentration of cyanide used in all of the experiments was 1/5000 molecular. The time of exposure varied in different experiments, but was constant for the three sets of pieces in any experiment. In the experiments recorded in table 1 the pieces were subsequently dried on filter paper and weighed, while in those in table 2 this procedure was omitted, the sole purpose of these experiments being to

determine the effect of potassium cyanide on pieces from different levels, the differences in rate of oxygen consumption per unit weight having already been determined by a large number of experiments.

The results of all of the experiments performed are recorded in the accompanying tables. In table 1 the rate of oxygen consumption is expressed as the fraction of a cubic centimeter of oxygen consumed by one gram of tissue in one hour, as calculated from the weight of the pieces and the total amount of oxygen consumed during the experiment.

TABLE 1

EXPERIMENT NO.	PIECES	NORMAL RESPIRATION	KNC RESPIRATION	PER CENT DEPRESSION	TIME	TEMPERATURE
					minutes	°C.
9	a	0.0611	0.041	32.9		
	b	0.039	0.0291	25.4	81	9.0
	c	0.079	0.043	45.6		
10	a	0.0404	0.0232	42.4		
	b	0.034	0.0265	22.1	91	9.5
	c	0.055	0.0271	50.9		
11	a	0.0468	0.0175	62.7	73	10.0
	b	0.0334	0.0184	44.9		
12	a	0.0577	0.0225	61.1		
	b	0.0437	0.0241	44.9	82	13.0
	c	0.0835	0.0368	55.9		
13	a	0.0402	0.0208	48.3		
	b	0.0354	0.028	20.9	80	13.0
	c	0.0749	0.0387	48.4		
7	a	0.0623	0.035	42.3		
	b	0.0383	0.0226	41.0	60	12.5
	c	0.050	0.0225	55.0		

In table 2 the respiratory rate is expressed as the total amount of oxygen consumed by the lot of pieces in one hour. In the tables the anterior pieces are designated by *a*, the middle pieces by *b* and the posterior pieces by *c*.

It is quite evident from the figures given in the tables and from the accompanying graphs (figs. 1 and 2), that the differences in respiratory rate of the pieces from different levels of the body are greatly diminished, or even partially reversed, by the difference in degree of

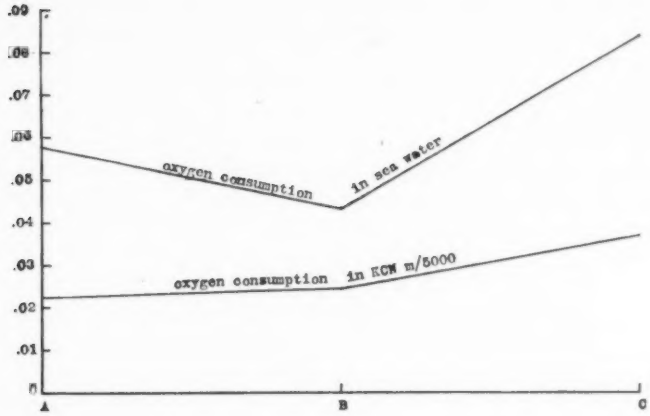
depression of the respiratory process produced by exposure to KNC m/5000 for from 60 to 91 minutes. There is considerable variation in the amount of difference in respiratory rate of the pieces from different levels in different experiments. Where these differences are great, it will be seen that the differences in degree of depression are correspond-

TABLE 2

EXPERIMENT NO.	PIECES	NORMAL RESPIRATION	KNC RESPIRATION	PER CENT DEPRESSION	TIME	TEMPERATURE
					minutes	°C
8	a	0.278	0.0872	68.7		
	b	0.229	0.142	37.9	70	12.0
	c	0.153	0.0453	70.4		
6	a	0.314	0.1844	41.28		
	b	0.243	0.1864	23.3	84	13.0
	c	0.201	0.0963	52.1		
14	a	0.418	0.2334	44.17		
	b	0.257	0.1975	23.9	90	12.7
	c	0.196	0.0875	55.36		
15	a	0.361	0.1913	47.01		
	b	0.213	0.1293	39.3	80	12.3
	c	0.240	0.110	54.17		
16	a	0.223	0.109	51.1		
	b	0.1022	0.0734	28.18	80	11.4
	c	0.0877	0.0349	60.2		
18	a	0.659	0.405	38.55		
	b	0.546	0.438	19.78	75	13.2
	c	0.327	0.175	46.5		

ingly large. This point is well illustrated by a comparison of figures 1 and 2.[1] In the experiment (*12*) graphed in figure 1 the differences in respiratory rate of the three sets of pieces are greater than in that (*10*) represented in figure 2, and the differences in amount of depression by cyanide are correspondingly greater in the former case. The same general relation between respiratory rate and the degree to which it

[1] In all of the graphs the abscissae represent the level of the pieces in the body and the ordinates, the amount of oxygen consumed in one hour by 1 gram of tissue, as determined by the weight of each lot of pieces and the total amount of oxygen consumed by it during the experiment.


.09
.08
.07
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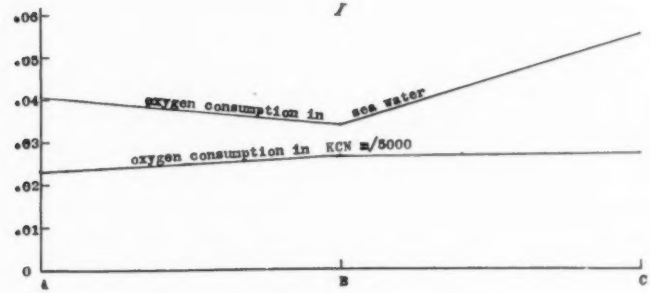
oxygen consumption in sea water
oxygen consumption in KCN m/5000
A
B
C

1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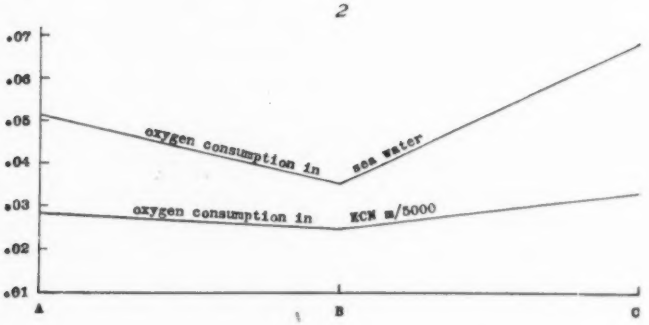
oxygen consumption in sea water
oxygen consumption in KCN m/5000
A
B
C

2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oxygen consumption in sea water
oxygen consumption in KCN m/5000
A
B
C

3

is lowered in the presence of cyanide is shown when the averages of the normal respiratory rates of all of the sets of pieces from each level of the body are compared with the averages of their respiratory rates in the presence of potassium cyanide. This point is graphically illustrated by figure 3.

The experimental results also suggest that the effect of 1/5000 molecular cyanide solution is probably not cumulative after 60 minutes exposure. However, successive determination of oxygen consumption after exposure to cyanide were not made.

DISCUSSION

It has been shown in this paper that the degree to which potassium cyanide depresses the respiratory processes in *Nereis* is dependent upon, and approximately proportional to the normal velocity of these processes. This result substantiates the conclusion, reached by members of this laboratory, that susceptibility to cyanide is an indicator of respiratory rate.

One of the most important lines of evidence which has led Child and other investigators in this laboratory to conclude that the graded differences in metabolic rate, which are characteristic of the axes of organisms, are the primary ordering factors in axiate differentiation is that derived from the experimental modification of development and regeneration. Child (7), (8), (9), (10), Hyman (4), (11) and Bellamy (12) have shown that in concentrations of toxic substances above the limit of acclimation, the regions of developing organisms which are highly susceptible to lethal concentrations, and hence are characterized by a high metabolic rate, are more greatly inhibited in development than are regions which are killed more slowly in high concentrations, and are therefore less active. The changes produced by increasing degrees of inhibition represent progressive steps in the reduction of regions of high metabolic rate as compared with less active regions, until forms completely devoid of axial differentiation are produced by extreme differential inhibition. The same statement also holds true in general for regeneration. When acclimation occurs after slight differential inhibition, the regions of high activity are the first to acquire tolerance, and changes the reverse of those occuring in differential inhibition take place (8), (9). As the regions of high metabolic rate are more highly susceptible to lethal concentrations of the same agents, these investigators have concluded that very probably, lower concentrations also produce a relatively great effect upon such regions, with the result that, as the concentration of the chemical agent increases

the gradients are gradually obliterated, and therefore that when the metabolic gradients are altered by the action of external factors, axiate organization is correspondingly affected.

The experiments on *Nereis*, which are presented in this paper, show that the axial gradient in respiratory rate which is characteristic of the major axis of this form is partially or wholly obliterated by the differential action of potassium cyanide, an agent by which both of the described types of morphological change have been produced. This evidence therefore strongly indicates the correctness of the view advanced by these workers on the basis of data obtained by other methods.

A complete discussion of the evidence concerning the origin and significance of the axial metabolic gradients has been given in a recent paper by Child (2).

SUMMARY

1. The rate of respiration in *Nereis vexillosa*, as indicated by oxygen consumption, is decreased in the presence of potassium cyanide in the concentration used (m/5000). The reduction of respiratory rate is greater in regions of the body in which respiration normally proceeds at a high rate than in those of low respiratory activity. The result of this differential action is the partial or total obliteration of the gradient in respiratory rate which has been found to be characteristic of the major axis of this form.

2. Since, under similar conditions, axial differentiation is modified in the same manner, this result substantiates the conclusion that the axial metabolic gradients are primary ordering factors in the determination of axiate organization. The data presented here also form further evidence that susceptibility to potassium cyanide may be used as an indicator of metabolic rate, at least as concerns the respiratory processes.

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

VI. Further Observations on the Denervated Heart in Relation to Adrenal Secretion

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In 1919 there was published from this laboratory a paper on the denervated heart as an indicator of an increased adrenal secretion (1). That paper and, indeed, all previous papers published from this laboratory, presenting the evidence for a specially stimulated or increased secretion of the adrenal glands, have been criticised by Stewart and Rogoff (2), (3). To answer their criticisms point by point would require much space and, because of detailed discussion of minor points, might lead to confusion rather than clarification. It is important to keep prominent the main question—Is there a secretion or an augmented secretion by the adrenal medulla evoked under conditions arousing sympathetic impulses, or is there always a fairly constant output, as Stewart and Rogoff claim? In the papers mentioned above evidence was offered that afferent stimulation, asphyxia and emotional excitement, which are modes of exciting sympathetic impulses, would each call forth a secretion of adrenin. In order to avoid diffuseness and arguments over trifling points, we propose for the present to narrow the question by limiting the mode of exciting sympathetic impulses to afferent stimulation alone. As has been said, all of the conclusions as to an augmented flow of adrenin stand or fall together (2, p. 363); if the evidence is made clear that there is additional adrenal discharge in consequence of afferent stimulation, it may be unnecessary to give further evidence that asphyxia and emotional excitement likewise increase the output.

The logic underlying the use of the denervated heart as an indicator of adrenal secretion is that this organ, no longer directly subject to nervous impulses, can be influenced only by agencies acting through

the circulation. It is highly sensitive to circulating adrenin. Afferent stimulation causes the heart, disconnected from the central nervous system, to increase to a marked degree its rate of beat. In the published reports the increments ranged from 24 to 52 beats a minute. After the adrenal glands were removed, there was no increase of rate or only a slight increase. Control curves were published showing that with a rise of blood pressure the rate was not augmented.

The logic of Stewart and Rogoff's criticism rests on the observation that after the heart is denervated afferent stimulation causes an increase of rate, not only when the adrenal glands are undisturbed in the body, but also after they have been removed. They made no attempt to explain the effects they noted after adrenalectomy, but drew the conclusion that the "heart reaction has no significance" and declared "baseless" the whole argument built upon it. Before granting this conclusion, we proposed to inquire into the amount of increase of the heart rate on afferent or splanchnic stimulation with the adrenal connections intact and after adrenal removal, then to analyze the conditions which may affect the heart, and, finally, after eliminating the factor which produces the results obtained by Stewart and Rogoff, to examine the results of afferent stimulation.

THE AMOUNT OF INCREASE OF THE HEART RATE WITH THE ADRENAL CONNECTIONS INTACT AND AFTER ADRENAL REMOVAL. In partial support of their claim that the acceleration of the heart is not a reaction serviceable in estimating the output of adrenin from the adrenals, Stewart and Rogoff cite two classes of cases which it will be necessary to eliminate, i.e., those in which the adrenals remained in the body with their large vein clipped, and those in which one gland was removed and the other deprived of splanchnic innervation. It had previously been pointed out that under neither of these circumstances could there be assurance that adrenal secretion was completely eliminated (1). Cases 190 and 191 in Stewart and Rogoff's series confirmed this conclusion by proving that clipping of the vein may not prevent an escape of the secretion into the circulation; and case 215 proved that section of the splanchnic nerves may not abolish all the secretory fibers. Since these facts are established, the only satisfactory way of dealing with the data reported by Stewart and Rogoff is to compare their results obtained when the adrenal glands were connected with the circulation and normally innervated, with their results obtained after removal of the glands.

In table 1 are presented figures showing the distribution of the maximal increases of heart rate due to splanchnic or reflex stimulation, before and after adrenalectomy, as obtained by Stewart and Rogoff (A) and by us (B). In both series, the observations were made on cats anesthetized with urethane or ether. In our series there were 48 different cases. The same range of stimulation was used with adrenals intact and after their removal. The length of stimulation varied from 10 to 45 seconds, but usually it lasted 30 seconds.

TABLE 1

Distribution of maximal increases of heart rate due to splanchnic or reflex stimulation, before and after adrenalectomy. A, Stewart and Rogoff's series; B, our series

INCREASE OF HEART BEATS PER MINUTE	NUMBER OF CASES			
	(A)		(B)	
	Adrenals in	Adrenals out	Adrenals in	Adrenals out
0				25
1– 5	4	22	1	46
6–10	15	30	3	69
11–15	6	11	8	13
16–20	6	4	17	7
21–25	13	3	20	2
26–35	18	5	21	1
36–45	7	3	23	
46–55	2		8	
56–70			3	
Totals.....	71	78	104	163

The chief discrepancy between the two sets of results is in the small accelerations of beat when the adrenals were present. Only 11.5 per cent of our cases (12 cases) had increases of less than 15 beats per minute whereas 35 per cent of Stewart and Rogoff's cases (25 cases) lay in that range. The small accelerations (below 11 beats per minute) in our series were in three instances due to reflex stimulation under very deep ether anesthesia, and in one instance to an unusually weak stimulus. It is noteworthy that according to Stewart and Rogoff's protocols the first stimulations were often weak, and that later they were stronger, a procedure which accounts to some degree for their more numerous instances of the pulse being faster by only 15 beats or less. Apart from this difference, the two sets of results tell the same story. Before

removal of the adrenals 65 per cent of Stewart and Rogoff's pulse accelerations and 88.5 per cent of ours were greater than 15 beats per minute. And after adrenalectomy, 80 per cent of their observations (63 out of 78) and 94 per cent of ours (153 out of 163) showed a heart rate increased less than 16 beats. These figures do not permit accepting as a general rule Stewart and Rogoff's statement that "a good acceleration, even as great as that obtained with intact adrenals, can be observed when they have been removed" (2, p. 305). Indeed, though the pulse may be accelerated by reflex or splanchnic stimulation after the adrenals are excised, the acceleration is, as a rule, to a quite different and much lower degree than that seen when the glands are present. The average increase of rate with normal adrenal connections, in our 104 observations, was 29 beats per minute. After adrenal removal, in our 163 observations, it was only 6 beats per minute; and in Stewart and Rogoff's 78 observations it was 11.

Although the rate of the denervated heart is usually increased to only a relatively slight degree by nerve stimulation after removal of the adrenal glands, there are instances of noteworthy acceleration, as shown in table 1, in both series of cases. In the former study (1) no such extreme instances appeared, though increments of 4 beats were reported. One might argue that since only rarely after adrenal excision can the pulse be accelerated to a degree comparable to that which can be produced before the excision, a reflex output of adrenin is proved. In employing the denervated heart as an indicator of adrenal secretion, however, it is desirable to have assurance that the organ is not being subjected to disturbing conditions other than those established for experimental purposes. We must inquire, therefore, not only into the major, but also into the minor accelerations noted after adrenalectomy.

WHAT CONDITIONS MAY ACCELERATE THE DENERVATED HEART AFTER ADRENALECTOMY? Since the denervated heart is directly subject only to agencies acting by way of the blood stream, we may reasonably look for the explanation of an altered cardiac rate in physical and chemical changes in that stream. The faster rate from afferent stimulation after removal of the adrenals might be attributable to a rise of arterial pressure or to an alteration of venous pressure, or to improvement of a poor circulation, or to the arrival of warm blood from the abdomen, or to accessory adrenal tissue, or perhaps to a factor or factors hitherto unknown. Each of these possibilities will be considered.

Is it due to increased arterial pressure? Stewart and Rogoff state that there is nothing strange about an increased rate of the denervated

heart when the central end of the sciatic or the peripheral end of the splanchnic nerve is stimulated—"it is obviously dependent upon the better blood flow through the coronary arteries" (2, p. 362). They point out (2, p. 361) that "excellent heart reactions can be obtained in the absence of the adrenals, provided that good vascular reflexes, as evidenced by the change of blood pressure, are elicited," and they conclude that the rise of blood pressure is the one factor which seems most intimately related to the cardiac acceleration (2, p. 361).

In support of this view are cited the experiments of Johansson and of Guthrie and Pike. Johansson (4) raised arterial pressure by splanchnic stimulation and noted an increased rate of the denervated heart, but in these experiments the *adrenal connections were intact* and therefore the results have no bearing on the cause of the increased rate after removal of the glands. By raising arterial pressure, Guthrie and Pike (5) did, in fact, succeed in accelerating the frequency of the denervated heart *in situ*, but only on perfusing the heart after the circulation had been stopped for "comparatively long periods"—a condition which did not exist in any of Stewart and Rogoff's or our experiments. Besides these citations, Stewart and Rogoff mention one case (no. 190 in their series) in which a rise of 11 beats per minute occurred after clipping the thoracic aorta; again, however, the experiment was not clean, for one adrenal was present, and the possibilities of its being stimulated by anemia and some of its secretion being borne to the heart were not ruled out. That these possibilities may be realized was proved in our experience when we noted delayed increases of rate under these circumstances which did not occur after both adrenals had been removed.

Opposed to this evidence on which Stewart and Rogoff have based their claim is a large array of testimony from various observers. Martin (6) reported that within very wide limits changes in arterial pressure have no influence whatever upon the rate of the heart isolated from all other bodily organs except the lungs. Magrath and Kennedy (7) found that the frequency of contraction of the isolated heart is largely independent of the volume flow in the coronary arteries. According to MacWilliam (8), when the heart with circulation intact is disconnected from the central nervous system, the rate of beat shows a decided insensitiveness to changes of blood pressure between 40 and 160 mm. Hg. Using the denervated heart *in situ* just as we have used it, Guthrie and Pike (5) reported "either no change in the pulse rate (with variation of pressure), or an increase of rate with a fall in pressure, or a decrease

in rate with rise in pressure." In Lehndorff's observations (9) increase of aortic pressure varying in amount and rapidity accelerated the denervated heart seldom or to only a slight degree. And Knowlton and Starling (10) noted that the rate of the isolated heart was not changed by shifts of pressure between 20 and 200 mm. Hg.

We have made 32 observations on 7 different animals with heart denervated and with adrenals removed. A thread was looped around the aorta low in the thorax and passed out through a small glass tube fastened in the chest wall. By pushing the tube inward while pulling on the thread it was possible to vary at will the arterial pressure in the anterior part of the animal. Thus the pressure was increased by amounts varying between 27 and 97 mm. Hg., starting from initial levels which ranged from 30 to 156 mm. Hg. In sixteen instances the increase was gradual; in nineteen it was abrupt. The elevation of the pressure lasted in different observations from 10 to 115 seconds. Neither the initial level, nor the abruptness nor gradualness of the rise, nor the duration had any uniform influence on the results. In ten cases the rate did not change; in thirteen cases it decreased (in seven of them only 1 or 2 beats); in nine cases it increased. Of these nine instances of accelerated rate three showed a rise of 1 beat per minute, one 2 beats, two 3 beats, and three 4 beats. And that was the limit. In table 2 is given the protocol of a typical experiment.

The foregoing facts give no support whatever for Stewart and Rogoff's claim that rise of arterial pressure and better blood flow through the coronary arteries occasion the faster rate of the denervated heart. We are forced by these facts to conclude that the acceleration is not due to increased arterial pressure.

Is it due to changes in venous pressure? Stewart and Rogoff remark that the mechanical conditions under which the heart works when the central end of the sciatic or the peripheral end of the splanchnic is stimulated are very different from those produced by compressing the aorta, "particularly as regards the venous inflow" (2, p. 362). Their suggestion that the rate may be affected by alterations of venous pressure they do not substantiate by any facts. Nor have we made observations on this point. It is sufficient, however, to cite MacWilliam (11) and Knowlton and Starling (10). The former states that marked changes in venous pressure, like changes in arterial pressure, were ineffective in changing the rate of the heart disconnected from the central nervous system; and the latter investigators, on the basis of

their study of the isolated heart, testify that they "were unable to produce alterations in frequency by even extreme changes in venous pressure." Figures confirmatory of these statements are given by Patterson, Piper and Starling (12). The facts do not permit us, therefore, to attribute the faster rate of the denervated heart to alterations of venous pressure.

Is it due to improvement of a poor circulation? Long ago Martin called attention to the fact that if the arterial pressure is reduced to less than 20 mm. Hg., the rate of the denervated heart, though unchanged for a minute or more, may soon become slower, an effect

TABLE 2

November 16. Cat, heart denervated, adrenals removed, loop around aorta low in thorax

PREVIOUS BLOOD PRESSURE	RISE OF BLOOD PRESSURE			PULSE PER MINUTE		
	Onset	Extent	Duration	Before rise	During rise	Change
mm. Hg.		*mm.* Hg.	*seconds*			
156	Abrupt	55	10	192	192	0
134	Abrupt	64	20	170	165	−5
123	Abrupt	62	15	162	162	0
121	Abrupt	39	20	160	159	−1
94	Abrupt	54	25	157	158	+1
78	Abrupt	86	30	160	158	−2
59	Abrupt	56	30	177	172	−5
60	Abrupt	71	25	172	166	−6
77	Abrupt	55	30	162	160	−2
36	Gradual	94	65	156	149	−7
					154	−2
67	Abrupt	39	30	154	154	0

which he attributed to deficient nutrition of the cardiac muscle. Later MacWilliam (11) noted that with a low arterial pressure (e.g., 30 mm. Hg.), the heart swells, and then a rise of pressure is accompanied by acceleration. In accord with this result is Guthrie and Pike's testimony (5) that after stopping the circulation "for comparatively long periods" the heart rate will vary with arterial pressure. It appears to be clear that the isolated heart, damaged by inadequate blood supply, may exhibit a faster rate as the blood supply is increased.

Markwalder and Starling (13) found that when the systolic pressure falls below 80 mm. Hg., the cardiac contraction begins to weaken—an

effect attributed by Bayliss (14) to an insufficient supply of oxygen, "an important fact to be remembered in experimental work." Of 174 observations reported by Stewart and Rogoff 116 were made on hearts previously subjected to blood pressures below 80 mm. Hg.—in some instances as low as 40 or 50 mm. It seemed possible that the faster rate noted in their experiments might be accounted for by the betterment of a deficient circulation. We found, however, that even when, because of the operative procedure, arterial pressure fell and remained below 50 mm. Hg. for more than 45 minutes, a rise of the pressure through 65 mm., lasting 30 seconds, accelerated the pulse only 4 beats per minute (cf. also table 2). Other experiments corroborated this one. It may be that in some cases of persistent low pressure, especially those associated with asphyxia, an improved oxygen delivery, such as would result from faster flow in the coronary arteries, would permit more rapid action in the needy tissue. The evidence in hand, however, does not allow us to ascribe an important rôle to this factor in those experiments of Stewart and Rogoff that involve sciatic and splanchnic stimulation.

Is it due to warmer blood from the abdomen? After examining the factors regulating the beat of the isolated heart, Patterson, Piper and Starling (12) remark, "In our preparation the rhythm of the heart is determined entirely by the local condition of the heart muscle and is a function simply of the temperature of the pacemaker." Earlier, also, Knowlton and Starling (10) had concluded that "the rate of the isolated heart fed with normal oxygenated blood is determined entirely by temperature, being unaltered by changes within wide limits either of arterial resistance or venous pressure." In the absence of the adrenal glands it seemed possible that the faster rate might be the consequence of warmer blood coming to the heart from the abdomen. The abdominal viscera, especially the liver, are known to be warmer than the thoracic (15), and a sudden flush of blood from a warmer region to the heart would surely accelerate the beat. Furthermore, if the animal were kept warm by a heating pad and the blood flow were sluggish because of low pressure, a faster flow through the vessels of the limited warmed area, accompanying the rise of pressure from nerve stimulation, might suddenly bring to the heart a flood of warmer blood and evoke a more rapid beat. In three of our cases, splanchnic stimulation after adrenalectomy accelerated the denervated heart only 4 beats per minute or less before any heat was applied, and the same stimulus after appli-

cation of a very warm heating pad induced increases as high as 8 and 10 beats per minute—increases which disappeared on removal of the pad. Though these experiments were promising as a means of accounting for the faster pulse after adrenal removal, they soon proved inadequate. A delicate thermometer introduced into the right auricle through the right jugular vein and the superior vena cava registered maximal changes of not more than 0.5°C. The greatest increase of rate of the isolated heart reported by Knowlton and Starling (10) for a rise of a full degree Centigrade was 15 beats per minute, and usually the increase was much less (6 beats). Since increases far larger than 15 per minute had to be explained (see table 1), obviously the slight rise of temperature in the cardiac blood was sure to prove insufficient. Moreover, in the course of further experimenting, cases appeared in which splanchnic stimulation accelerated the pulse in unwarmed animals deprived of their adrenals quite as much as it did in the warmed. Though local heating may be a condition for a faster beat when the denervated heart is left *in situ* and when the circulation is shifted by local vascular stimulation or reflexes, its effect, according to the facts in our possession, is slight. We are not justified, therefore, in attributing the more rapid rate after adrenalectomy to warm blood coming to the heart.

Is it due to accessory adrenal tissue? Stilling (16), Kohn (17) and Vincent (18) have described thin bands or fine threads of chromaffine tissue along the ventral side of the abdominal aorta in the dog, cat and rabbit. In the dog the main structure is surrounded by connective tissue containing vessels and nerves. Vincent proved that extracts of this tissue have the usual effect of adrenin in raising blood pressure. Might it not be true that after adrenalectomy splanchnic stimulation evokes from this accessory adrenal structure a secretion which makes the heart beat faster? To test this possibility animals were used in which, after excision of the adrenals, splanchnic stimulation increased the heart rate between 12 and 18 beats per minute. The region where the accessory adrenal tissue is found was then either massaged, or dissected wholly clear of everything except the large blood vessels. Massage is a very effective means of bringing the adrenal medulla into activity; but when applied to the area where the accessory tissue is found, massage did not have any influence in producing a cardiac acceleration. And after thorough dissection of this area splanchnic stimulation still caused a faster beat of the denervated heart. Consequently we cannot rely on extra-adrenal chromaffine structure to

explain the faster rate. Against that explanation also is Stewart and Rogoff's testimony as to the discrepancy between the responses of the heart and the pupil. If after exclusion of the adrenals the faster pulse which follows nerve stimulation were due to a secretion from accessory adrenal tissue, the sensitized pupil should respond along with the heart. That, however, does not occur. The facts force the conclusion, therefore, that the cardiac acceleration is not the result of activity in outlying bands or threads of chromaffine tissue.[1]

Is it due to a factor or factors hitherto unknown? The foregoing enquiries and observations have offered no explanation for the more rapid cardiac beat produced by nerve stimulation after adrenal removal. It is not due to variations of mechanical pressures, either arterial or venous; it is not due to warmer blood from the abdomen, nor to aberrant adrenal tissue. Indeed, the original basis for using the denervated heart to indicate adrenal secretion—i.e., that the heart, released from nervous control, is remarkably indifferent to other than chemical agents in the blood—has been proved to be thoroughly sound. Since the cardiac beat may be accelerated by splanchnic stimulation after adrenalectomy, however, it is a fair inference from all the facts before us that some other chemical agent than adrenin, carried by the blood to the heart, is responsible for the faster cardiac rate. Elsewhere (19) the conditions under which this agent is evoked are described. For present purposes it is sufficient to show that severance of the nerves in the mesentery or merely the nerves accompanying the hepatic artery wholly or very nearly eliminates the effect.

In the following figures are presented successive changes in heart rate (H.R.) per minute resulting from successive splanchnic stimulations (usually 30 seconds; coil position usually 8 cm.), before removal of the adrenal glands, after adrenalectomy, and after section of the hepatic

[1] In an effort to exclude adrenal tissue atropine sulphate (1 per cent) was repeatedly given intravenously until no increase of the heart rate occurred on stimulating the splanchnic nerve. At that stage, however, there was no response of the splanchnic blood vessels. It was impossible, therefore, to be sure that the drug had not blocked the nerve impulses to both the adrenals and to the blood vessels.

It seemed possible that a chrome salt might affect adrenal tissue injuriously before disturbing other tissues. Sodium chromate (3 per cent) was repeatedly injected until the blood pressure was much reduced, without, however, any interference with cardiac acceleration on stimulating the splanchnic.

nerves; the figures in the second row for each date show the attendant increases of blood pressure (B.P.) in mm. Hg.:

		BEFORE ADRENALECTOMY		AFTER ADRENALECTOMY				AFTER SECTION OF HEPATIC NERVES				
January 8	H. R.	24	18	4	4	4		2	0	0	0	
	B. P.	30	35	40				55	45	25	35	
January 10	H. R.	42	42	6	8	6		1	2	0	0	2
	B. P.	70	75	50	40	45		14	24	14	10	12
January 11	H. R.	24	40	6	4	10		2	2	0	0	
	B. P.	34	46	30	44	60		44	56	34	34	
January 15	H. R.	50	64	8	8	8	12	2	0	2	0	
	B. P.	56	70	54	74	70	60	50	47	27	34	

That the same effects appear when the sciatic rather than the splanchnic is stimulated is shown by the following figures. (The hepatic nerves were cut at the same time that the adrenals were removed, hence the absence of results for adrenal removal alone.)

		BEFORE ADRENALECTOMY			AFTER ADRENALECTOMY AND HEPATIC NERVE SECTION	
January 18	H. R.	48	24	30	0	
	B. P.	40	6	13	11	
January 31	H. R.	46	34		0	2
	B. P.	20	16		10	10

Severance of either the hepatic or the mesenteric nerves can be done without interfering with the nerve supply to the adrenal medulla. Thus it is possible to secure a practically pure adrenal response from splanchnic stimulation. With this preparation further evidence regarding the influence of afferent stimulation on adrenal secretion was obtained.

FURTHER EVIDENCE FOR REFLEX ADRENAL SECRETION. Stewart and Rogoff have themselves furnished part of the data proving that adrenal secretion can be increased greatly by stimulating the splanchnic nerves (20), and they have adduced evidence that certain drugs (e.g., strychnine), known to excite sympathetic impulses, will augment the adrenin

output (21). Their belief, therefore, that the adrenal discharge is continuous and constant involves the unique conception that there exists in the body a secretory mechanism which though subject to nervous control and capable of increased output on nervous stimulation, nevertheless manifests only an unvarying tonic activity. Various other observers, using denervated limb and kidney (22), salivary gland (23), chromatophores (24), and heart (1), have noted in these denervated organs reflex effects such as are produced by injecting adrenin—effects which disappear when the adrenals are excised. Stewart and Rogoff deny that these results follow from increased adrenal secretion and explain them as due to "redistribution of blood." This operates in two ways: *a*, That a rise of blood pressure increases the rate of flow through the denervated region and thus the rate of adrenin delivery (25); and *b*, that reflex vasoconstriction, especially splanchnic, causes slowing of the flow in the inferior cava and thus increased concentration of adrenin in the caval blood (3, p. 551).

For the establishment of their own doctrine it is essential for Stewart and Rogoff to explain away the evidence that adrenal secretion can be increased. If "redistribution of blood" and resultant concentration and redistribution of adrenin do not account for the positive evidence of increased secretion, the conclusion warranted by the facts would be that the secretion can be increased. Thereupon Stewart and Rogoff's dictum that it continues unaltered by sympathetic reflexes would be proved to be incorrect, and their procedure, yielding only negative evidence, would be condemned.

Does "redistribution of blood" adequately explain away the positive evidence? This question which is fundamental to their claims, Stewart and Rogoff have not attempted to answer. For testing reflex effects they have used an operative procedure different from that used by all other investigators, and in connection with it they have employed quantitative methods to estimate the adrenin output. They have not employed quantitative or any other experimental methods, however, to justify their criticism of investigators whose positive results are irreconcilable with their negative results.

They have superposed quantitative methods on the unproved assumption that their own procedure, revealing no evidence of reflex secretion, is correct and that other procedures, yielding evidence of a reflex secretion, are so defective as to be unworthy of credit. By appropriate experiments, it is possible to test whether the "redistribution of blood" consequent upon afferent stimulation has the explanatory value which they have ascribed to it.

The effect on the heart rate of afferent stimulation in animals with minimal vascular reflexes. One way to test the validity of Stewart and Rogoff's idea that "redistribution of blood" accounts for a faster cardiac rate is by use of what may be called a "reduced" animal. In this preparation both carotid, both brachial and both renal arteries were tied, the aorta was closed below the renals, and the nerve filaments in the mesentery were all severed. Thus the vascular area capable of responding reflexly was reduced to a minimum. For afferent stimulation the brachial nerve was used, close to the point where the brachial artery was ligated. Such stimulation was not capable of inducing a noteworthy redistribution of blood in the body because there was no considerable mass of vessels left to respond to vasoconstrictor impulses. The splanchnic area was eliminated, both as an agency for concentrating the blood in the inferior cava and as an agency for raising pressure and increasing the flow through the coronaries. In the abdominal cavity the only viscera which remained innervated by the splanchnics were the adrenal glands. Use of this preparation was attempted in the earlier employment of the denervated heart as an indicator of adrenal secretion, but only rarely could reflex effects be obtained from it (1, p. 427). In those experiments, however, urethane was the anesthetic. In the present series the animals were anesthetized with ether. It was found that though reflex effects were abolished or greatly reduced by deep etherization, a degree of moderate anesthesia could be established at which satisfactory reflex responses occurred. The results are presented in table 3 and are illustrated in the upper record of figure 4 (11 :07). The first three records of December 13 were made before the animal was "reduced" and resulted from sciatic stimulation. In all other instances the animal had been prepared as above described, and reflexes were evoked by exciting the brachial nerve for 30 seconds.

The figures in the last column of the table give the blood pressure changes at the end of stimulation. They were usually slight (in 17 cases out of 25, less than 10 mm. Hg.). As shown in figure 1, the maximal rise of pressure averaged 6 mm. Hg., and at the end of stimulation the pressure averaged 5 mm. below the original level, a drop that continued to 12.5 mm. at the end of 40 seconds. These figures are to be compared with average increases of 15.5, 12 and 4.5 mm. Hg. respectively in animals not reduced. And yet in both conditions the increase of heart rate was approximately the same. In the separate experiments likewise no difference of effect on the heart was noted, whether the blood pressure at the end of stimulation was raised or lowered or left practically unal-

TABLE 3

Reflex increases of heart rate, with various blood-pressure changes, in "reduced" animals, i.e., with carotid, brachial, and renal arteries and lower aorta tied, and with mesenteric nerves cut

DATE	STIMULATION		COIL POSITION	HEART RATE PER MINUTE		INCREASE OF RATE	ARTERIAL PRESSURE		CHANGE
	Time	Nerve		Before stimulation	Just after		Before stimulation	Just after	
							mm. Hg.	mm. Hg.	mm. Hg.
December 7	11:28	Brachial		252	291	39	100	98	− 2
	11:33	Brachial		243	282	39	92	88	− 4
	11:37	Brachial		228	266	38	55	60	+ 5
December 8	12:34	Brachial	(7)	200	216	16	141	135	− 6
	1:00	Brachial	(7)	207	228	21	146	135	−11
December 9	11:01	Brachial	(7)	222	237	15	125	123	− 2
December 10	10:30	Brachial	(6)	216	234	18	159	150	− 9
	10:44	Brachial	(4)	204	222	18	114	110	− 4
	10:57	Brachial	(6)	225	258	33	166	160	− 6
	12:14	Brachial	(6)	216	246	30	111	127	+16
December 11	10:12	Brachial	(7)	213	243	30	124	108	−16
	10:23	Brachial	(5)	204	234	30	104	85	−19
	11:04	Brachial	(5)	192	234	40	81	76	− 5
	11:52	Brachial	(6)	186	204	18	78	76	− 2
	11:59	Brachial	(5)	174	204	30	78	76	− 2
December 13	*10:21	Sciatic	(7)	180	210	30	136	153	+17
	*11:23	Sciatic	(7)	192	204	12	102	98	− 4
	*11:28	Sciatic	(4)	192	216	24	106	120	+14
	12:07	Brachial	(4)	192	216	24	108	92	−16
	12:10	Brachial	(4)	192	228	36	88	90	+ 2
	12:47	Brachial	(4)	180	198	18	78	70	− 8
December 14	10:51	Brachial	(5)	216	252	36	128	100	−28
	11:14	Brachial	(5)	198	213	15	53	50	− 3
December 15	10:24	Brachial	(5)	240	274	24	96	102	+ 6
	10:34	Brachial	(5)	240	246	6†	112	92	−20
	10:38	Brachial	(5)	246	258	12	121	102	−19
December 16	10:42	Brachial	(5)	198	234	36	182	190	+ 8
	11:07	Brachial	(5)	195	234	39	141	144	+ 3

* Animal not "reduced."

† Very deep anesthesia.

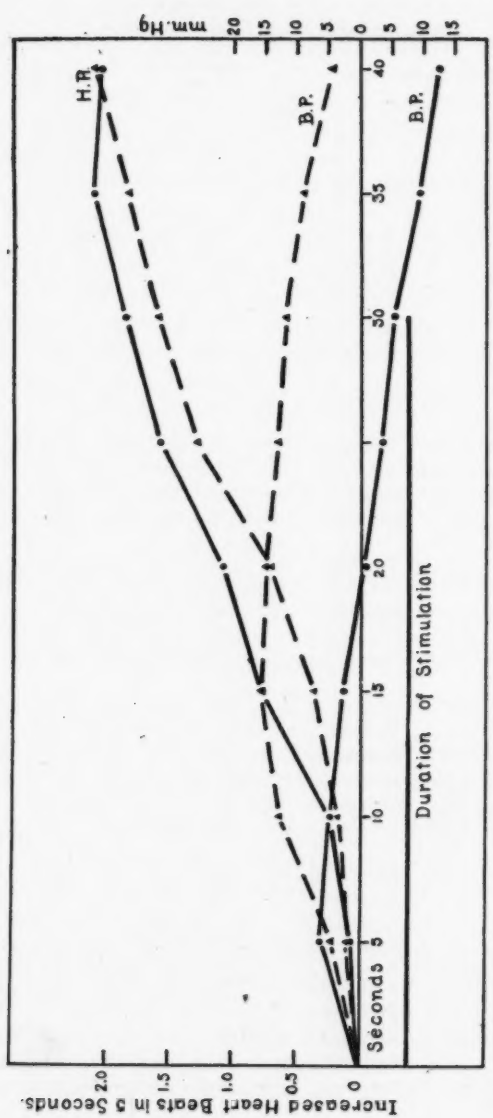

Fig. 1. Increases of heart rate and changes of blood pressure, recorded at 5-second intervals starting with 30 seconds' stimulation of an afferent nerve. The long-dash lines represent the average figures for 21 observations on "reduced" animals; the short-dash lines represent the average figures for 13 observations on animals not reduced.

tered. The heart rate was invariably accelerated—in al but 2 of the 25 cases (in which the anesthesia became very deep) by 15 or more beats per minute and in 13 of the cases by more than 30 beats. In other words, the increases of rate were of the same order as those seen when the adrenals were intact in the unreduced animal (cf. table 1). The figures for December 13 in table 3 illustrate similar facts; the heart rate was increased in quite the same way without regard to whether the blood pressure was reflexly raised or lowered, or whether the circulation was complete or reduced to a minimum. If the results had been modified in any degree, if the faster rates of the heart had been in any recognizable measure less in the "reduced" than in the unreduced animals, there might be a possibility of giving a bit of credit to Stewart and Rogoff's claim of a "redistribution of blood" in the body. The experiments, however, do not permit that concession to be made.

Because Stewart and Rogoff have employed quantitative methods they urge that their results should be accepted rather than the results of others who have relied only on qualitative procedures. Quantitative methods, though desirable and important, yield data good only for the conditions prevailing at the time. They do not prove that the conditions were normal or even approached normal. Nor are quantitative methods the only means of securing *accurate* information. It would be absurd to argue that a carpenter's level is useless and untrustworthy because it does not measure quantitatively the degree of deviation from the horizontal. Its service is to tell whether deviation is present or not. The denervated heart, likewise, since unaffected by all except chemical changes brought to it in the blood stream, is, we submit, when used as we have used it, with the adrenals the only innervated abdominal viscera, a reliable and delicate instrument for detecting whether or not adrenin has been added to the circulating blood. There is nothing in the quantitative character of negative evidence that gives it dominance over positive evidence which is quite as accurate.

The effect on the heart rate of afferent stimulation during constant inflow of adrenalin, after removal of the adrenals. If after excision of the adrenals adrenalin is introduced into the femoral vein continuously and uniformly at the rate regarded by Stewart and Rogoff as normal, the condition is restored which prevailed before the excision. Now, if sciatic or brachial stimulation produces a rise of blood pressure similar to that which was produced before, the "redistribution of the blood" and the larger delivery or the greater concentration of the adrenalin, which Stewart and Rogoff have assumed to occur, should occur; and if their

TABLE 4

Reflex increases of blood pressure and heart rate with adrenals present; later in each instance, after adrenal removal, reflex increases of blood pressure, without increases of heart rate, though the formerly continuous adrenal secretion was being replaced by a continuous flow of adrenalin into the femoral vein. Uniform brachial stimulation, 30 seconds

DATE	TIME	ADRENALIN PER KILOGRAM PER MINUTE	HEART RATE PER MINUTE		INCREASE OF RATE	ARTERIAL PRESSURE		INCREASE
			Before stimulation	Just after		Before stimulation	Just after	
		mgm.				*mm.*Hg.	*mm.*Hg.	*mm.*Hg.
October 6	10:33		198	224	26	100	132	32
		Adrenals out	176					
	11:28	0.00066	200	200	0	112	138	26
	11:30	0.00066	192	194	2	120	138	18
	11:49	0.00066	192	194	2	116	134	18
	12:22	0.00066	190	190	0	114	130	16
October 7	10:44		176	196	20	106	126	20
	10:52		184	200	16	106	122	16
	10:56		180	200	20	108	122	14
		Adrenals out	162					
	11:37	0.00076	180	180	0	118	130	12
	11:50	0.00076	178	180	2	131	140	9
March 31	3:00		210	256	46	144	182	38
	3:04		210	242	32	150	178	38
	3:11		212	240	28	138	164	26
		Adrenals out	178					
	3:25		178	180	2	94	110	16
	4:48	0.001	224	224	0	150	177	21
	5:15	0.00068	214	216	2	132	154	22
	5:18	0.00068	212	212	0	132	160	28
	5:21	0.00068	210	208	−2	138	160	22
April 2	11:16		204	224	20	130	144	14
		Adrenals out	162					
	11:53		164	166	2	52	62	10
	11:59	0.00069	198	200	2	68	76	8
	12:08	0.0007	202	204	2	80	92	12
	12:09	0.0007	204	204	0	70	78	8
	12:10	0.0007	200	202	2	68	80	12

assumption is correct, the heart rate should be accelerated. Examples of this procedure are given in table 4. Observe the basal heart rate before excision of the adrenals, immediately after their excision, and during the inflow of adrenalin. In the cases observed on October 6 and 7 the

hepatic nerve filaments were not cut; on March 31 they were cut at the start of the experiment, and on April 2 they were cut immediately after the adrenals were excised. The adrenalin was introduced into the femoral vein from a burette. The fluid in the burette was under constant high pressure, and the outflow was regulated by a needle valve. The amounts per kilo per minute were within the range (0.0003 to 0.0008 mgm.) found normal for the cat by Stewart and Rogoff, when they made assays by reactions (eye, blood pressure) inside the body (26). It is of interest to note that after adrenal removal on October 6 the heart rate fell from 198 per minute to 176, and on October 7 from 180 to 162, on March 31 from 212 to 178, and on April 2 from 204 to 162. In each case the constant inflow of adrenalin at the rates shown in the table brought back the pulse to approximately the original rapidity. It is important to be sure that a steady rate has been established by the inflowing adrenalin before the reflex is tested.

The average output of the adrenals per kilo per minute, assayed by eye and blood pressure methods by Stewart and Rogoff, was 0.0006 mgm. adrenalin (approximately the amount shown in our table 4 to be requisite to reëstablish the heart rate prevailing before adrenal removal); this may be called their *interior* standard. The average output assayed by their use of intestine and uterus segments was less than half this amount (0.00025 mgm.); this is their *exterior* standard. "It is quite impossible," they state, "to explain this difference as due to accidental variations in the rate of output in the animals of the two series. It must, therefore, be concluded that some of the epinephrin is lost when the adrenal vein blood is drawn, in the interval which necessarily elapses, and under the manipulation which the blood necessarily undergoes before it is applied to the segments" (26). Is this loss of more than 50 per cent not worth considering? Why is adrenin "lost"? How rapidly is it "lost"? Is the same amount "lost" on all occasions? Is there is minimal limit to the loss? How valuable is a quantitative method when applied to a procedure which involves an undetermined loss of the material which is being assayed? These questions seem not to have been considered.

As inspection of table 4 will reveal, after adrenalectomy reflex increases of blood pressure occurred which were of the same order as those occurring before. The operation, therefore, did not injure the nerve supply of responsive vascular areas. Instead of the typical increase of heart rate, however, which was seen while the adrenals were present, there was, after their removal, either no increase whatever, or at most an insignificant rise of 2 beats per minute. In figure 2 are shown records

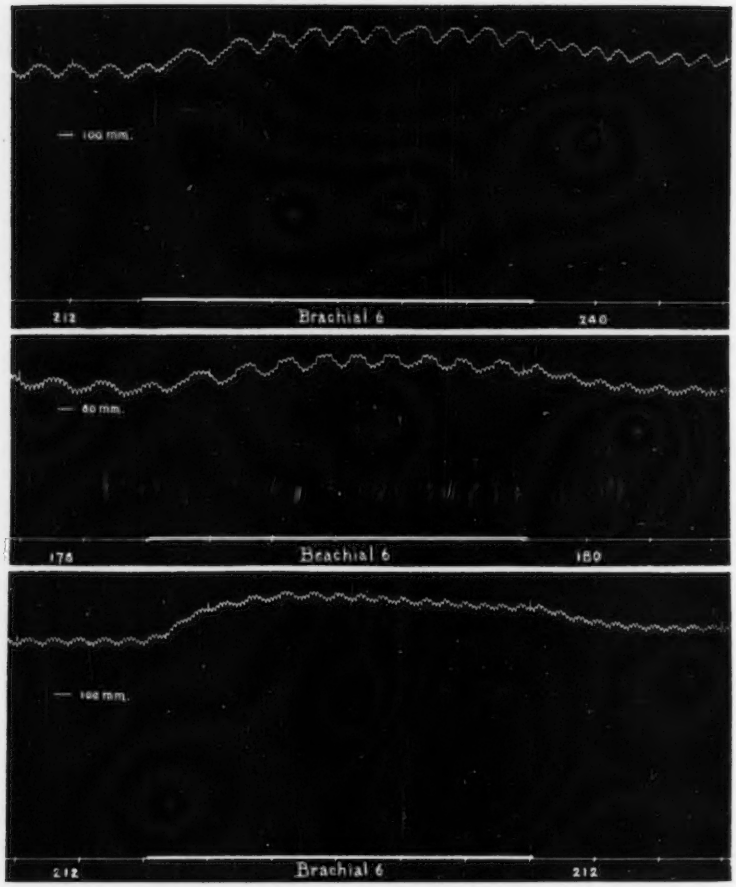

Fig. 2. Top tracing, 3:11, March 31, reflex increase of arterial pressure and cardiac rate (212 to 240 beats per minute, heart denervated and hepatic nerves cut) with adrenals present.

Middle tracing, 3:25, reflex increase of arterial pressure after adrenals removed. Cardiac rate, now reduced to 178 per minute, was increased to 180.

Bottom tracing, 5:18, reflex increase of arterial pressure, but no increase of cardiac rate, though restored to 212 beats per minute and there maintained by continuous steady inflow of adrenalin, 0:00068 mg. per kilo per minute.

Time-line, zero pressure; time here and in other records, 5 seconds.

of the effects of brachial stimulation, *a*, with hepatic nerves cut; *b*, after adrenalectomy; and *c*, while an inflow of adrenalin was replacing the constant secretion lost by adrenalectomy.

It seems hardly necessary to lay emphasis on the facts just presented. In every respect the conditions after adrenalectomy were what Stewart and Rogoff assume to be normal—a constant flow of adrenin into the inferior cava at the "normal" rate, and an afferent stimulation which by vascular reflexes raised blood pressure as before. The absence of any noteworthy acceleration of the heart rate under these circumstances is sharply opposed to their unsupported assumption that "redistribution of blood" and consequent shifts in the distribution of adrenin explain the faster beat.[2] Yet the faster rate resulted regularly when the brachial nerve was stimulated before the adrenals were excised. The conclusion which the facts force upon us is that this acceleration was due to a reflex increase of adrenal secretion.

The denervated heart as a means of quantitating adrenal secretion. According to Stewart and Rogoff, the denervated heart "cannot yield any information" regarding the rate of output of the adrenal glands (2, p. 359). The results of our observations show that this judgment is incorrect. We have found that when the "reduced" animal is used, repeated intravenous injections of adrenalin, in equal amounts and at a uniform rate, cause repeatedly the same or very nearly the same increases of heart rate. This is not so true of the unreduced animal, but appears when the circulation is simplified. The method is similar to that devised by Elliott (27), in which he simplified the circulation by pithing the central nervous system to the mid-thorax and then found that repeated injections of equal doses of adrenalin would produce equal rises of blood pressure. Elliott used this preparation to quantitate

[2] In a former paper one of us reported that when, during sciatic stimulation, the blood pressure is prevented from rising by compression of the chest, the heart rate nevertheless increases, and *does not increase more when the pressure is permitted to rise.* This effect did not occur when the same experiment was performed after adrenalectomy. The conclusion was drawn that the acceleration was due to reflex adrenal secretion and not to a "redistribution of blood," i.e, an increased flow through the coronaries, due to increased arterial pressure. Stewart and Rogoff have set up an elaborate argument (2, p. 359) directed towards showing that the effect is accounted for by concentration of adrenin in the impeded venous return. We have found, however, that if after adrenalectomy a constant passage of adrenalin into a vein is arranged, to take the place of the "constant normal secretion," compression of the chest to prevent rise of blood pressure during afferent stimulation does not cause an increased rate of the denervated heart, nor does the rate increase when thereafter the pressure is suddenly permitted to rise.

TABLE 5

Increase in heart rate, in "reduced" animal, resulting from intravenous injection of adrenal in (1:100,000), at uniform rate

DATE AND WEIGHT	TIME	INJECTION		INITIAL		INCREASE OF PULSE (5 SEC.) INTERVALS STARTING WITH INJECTION											
		Amount	Time	Blood pressure	Pulse (5 secs.)	1	2	3	4	5	6	7	8	9	10	11	12
		cc.	*sec.*	*mm.* Hg.													
October 18, 3.1 k...	12:05	0.25	5	98	19.0	0	1.5	2.5	3.5	3.5	2.5	2.5	1.5	1.5	1.5		
	12:11	0.25	5	102	19.0	0	0.5	1.5	3.0	3.5	3.5	3.0	2.5	2.5	2.0	1.5	1.5
	12:15	0.25	5	108	19.0	0	0.5	2.5	3.5	3.0	3.0	3.0	2.5	2.0	2.0	1.5	1.0
	12:20	0.25	5	102	19.0	0	0.5	1.5	3.0	3.5	3.0	2.5	2.0	2.0	1.5	1.0	1.0
	12:25	0.5	10	98	19.0	0	0.0	1.0	3.0	3.5	3.5	2.5	2.5	2.5	2.0	2.0	1.0
	12:29	0.5	10	92	19.0	0	0.0	1.0	2.5	3.0	3.0	3.0	2.5	2.0	2.0	1.0	1.5
	12:36	0.5	10	84	19.0	0	0.0	1.5	3.0	3.5	3.5	3.0	2.0	2.0	2.0	1.0	1.5
December 10, 4.4 k.....	1:06	0.3	20	112	19.0	0	0.0	0.5	1.0	2.5	3.0	3.0	2.5	2.0	2.0	1.0	1.0
	1:18	0.3	20	106	19.5	0	0.0	0.5	0.5	1.0	2.0	2.0	2.5	2.5	1.5	1.0	1.5
	1:34	0.3	20	76	19.5	0	0.0	0.0	0.5	2.0	3.0	2.5	2.5	2.5	2.5	1.5	1.5
	1:44	0.3	20	70	19.5	0	0.0	0.0	0.5	1.0	2.5	2.5	2.0	2.0	1.5	1.5	1.5
December 11, 3.2 k.....	10:43	0.3	15	92	17.5	0	0.0	1.0	2.0	2.5	2.5	2.5	3.0	2.5	2.5	2.0	2.0
	10:52	0.2	10	90	17.0	0	0.0	1.0	2.0	2.0	2.5	2.5	2.5	2.5	2.0	2.0	2.0
	12:10	0.3	13	50	13.5	0	0.0	0.0	0.5	2.0	3.0	3.5	3.5	3.5	3.5	3.0	3.0
	12:19	0.3	13	54	14.5	0	0.5	0.0	0.0	1.5	2.5	3.5	3.5	3.0	3.0	3.0	2.5
December 13, 3.5 k.....	12:14	0.3	15	98	15.0	0	0.5	1.0	2.0	2.5	3.5	3.5	3.0	3.0	3.0	3.0	2.5
	12:18	0.3	15	82	15.0	0	0.0	0.5	2.0	3.0	3.0	3.0	3.0	3.0	2.5	2.5	2.0
	12:24	0.125	15	90	15.0	0	0.0	0.5	1.0	1.5	2.5	2.0	2.0	2.0	1.5	1.5	1.5
	12:28	0.125	15	88	15.0	0	0.0	1.0	1.0	1.5	2.5	2.0	2.0	2.0	1.5	1.5	1.5
	12:34	0.4	15	90	15.0	0	0.5	1.5	3.0	3.5	4.0	4.0	4.0	3.5	3.5	3.5	3.0
	12:41	0.4	15	87	15.0	0	0.5	1.0	2.5	3.5	4.0	4.0	3.5	3.5	3.0	3.0	3.0

December 15, 4.1 k.....	10:44	0.23	15	96	20.0	0	0.0	0.0	0.5	0.5	1.0	1.0	1.0	0.5	0.5	0.0	0.0
	10:48	0.21	15	78	19.5	0	0.0	0.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	0.5	0.5
	11:01	0.5	15	86	21.0	0	0.0	0.0	0.0	1.0	1.0	1.5	1.5	1.5	1.0	1.5	1.0
	11:08	0.5	15	90	21.0	0	0.0	0.0	1.0	1.5	1.5	1.5	1.5	1.5	1.5	1.0	1.0
December 16, 3.8 k.....	11:15	0.41	20	145	17.0	0	0.0	0.5	1.0	*2.5	3.0	3.0	3.0	2.5	2.0	2.0	2.0
	11:24	0.41	20	116	16.5	0	0.0	1.0	1.0	3.0	3.5	3.5	3.5	3.0	3.0	2.5	2.5
	11:33	0.38	20	114	17.0	0	0.0	0.0	1.0	2.0	3.0	3.0	3.0	2.5	2.5	2.0	2.0

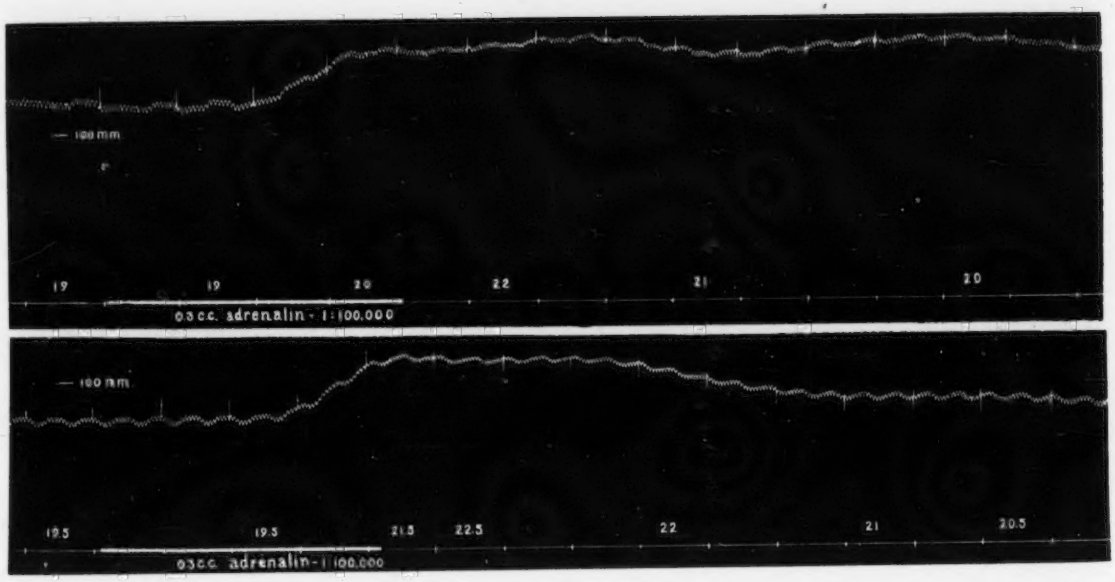

Fig. 3. Records (half-size) showing acceleration of the denervated heart of a "reduced" animal from injecting by vein in 20 secs., 0.3 cc. adrenalin, 1:100,000. See December 10, table 5. The effects are closely similar, though the initial pressures at 1:06 and at 1:34 were quite different.

unknown amounts of adrenin, and Folin, Cannon and Denis (28) proved that the results obtainable corresponded in accuracy to colorimetric observation. The main facts brought out by our observations are illustrated by the figures in table 5. Inspection of the table will reveal the following points:

1. Repeated equal doses of adrenalin injected intravenously at a uniform rate repeatedly produce in a given animal the same or nearly the same increases of heart beat. This is illustrated by the correspon-

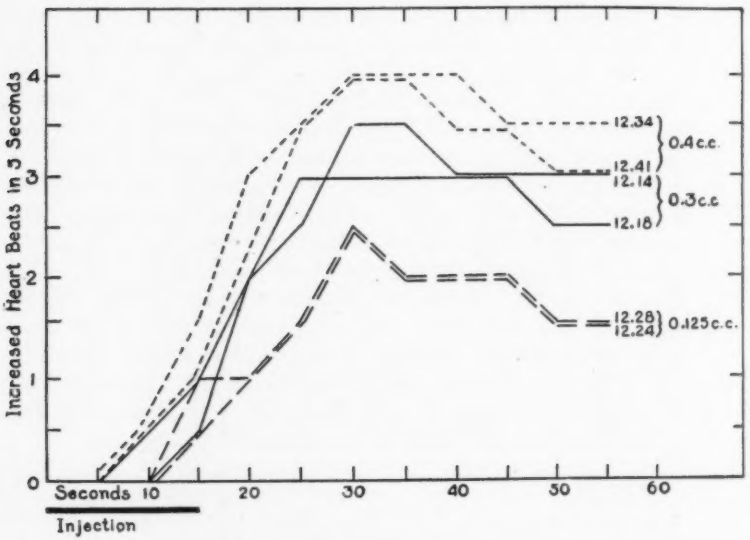

Fig. 4. Accelerations of the denervated heart produced by injecting by vein, into a "reduced" animal, adrenalin (1:100,000) at different rates. During 15-second periods different amounts—0.125 cc., 0.3 cc. and 0.4 cc.—were, in each instance, injected twice. See December 13, table 5.

dences in each of the eleven different dosages reported in table 5 (see also fig. 3). It is important that the injections to be compared be given at not too great an interval; e.g., on December 11, the first two tests made near together are consistent, and the last two likewise; but the two pairs of tests, separated by more than an hour, are not so closely consistent, though the rates of injection were approximately the same in all four cases. The maximal increase does not always appear at the same interval after the start of injection, nor last the same length

of time. The greatest variation of rate noted on repeating a dose has been 6 beats per minute (e.g., the difference between an increase of 30 and 36 or 36 and 42 beats per minute).

2. With such a weak dilution as we have employed (adrenalin 1:100,000), and with such small doses, increasing the amount while keeping the same rate of injection does not increase further the rate of the heart. For example, in the experiment of October 18 (table 5) 0.25 cc. adrenalin injected in 5 seconds caused an increase of 42 beats per minute; twice that amount (0.5 cc.) injected in twice the time (10 seconds) caused the same increase (42 beats). (Cf. also December 11, 10:43 and 10:52.)

3. As the injections differ in rate, the accelerations of the heart likewise differ in degree. For example, in the observations made December 13 (table 5) 0.3 cc. adrenalin injected in 15 seconds caused a maximal increase of 3.5 beats in 5 seconds; 0.125 cc. a maximal increase of 2.5 beats; and 0.4 cc. a maximal increase of 4 beats. (See fig. 4.) A similar difference is recorded in the experiment of December 15.

4. In so far as the effects of adrenalin injections are concerned the blood pressure variations in the reduced animal appear to be of minor importance. In the experiments of October 18 and December 10, e.g., there were at different times marked differences of blood pressure, and yet the effects of the same doses given at a uniform rate in each case were the same or nearly the same. A detail from the experiment of December 10 (see also fig. 3) is presented in the following figures, representing the heart beats and the arterial pressure (mm. Hg., *italicised*) for a series of 9 five-minute intervals starting with the injection:

	1	2	3	4	5	6	7	8	9
1:18	19.5	19.5	20.0	20.0	20.5	21.5	21.5	22.0	22.0
	106	*104*	*103*	*124*	*140*	*140*	*140*	*136*	*126*
1:44	19.5	19.5	19.5	20.0	20.5	22.0	22.0	21.5	21.5
	70	*72*	*76*	*96*	*110*	*110*	*112*	*108*	*98*

These results are in accord with the results reported in table 4, showing that when the pulse is being sustained at a faster rate by a constant inflow of adrenalin, a rise of blood pressure does not alter the rate. They are also in accord with the experiment which demonstrated that temporarily keeping the blood pressure down by thoracic compression and suddenly allowing it to rise has no effect on the rate of the heart when subjected to secreted or injected adrenin (see footnote, p. 327). There is no question that the accelerated beat recorded in table 5 is due

to adrenalin added to the blood stream. The inference which seems justified by the correspondence between the degree of acceleration and the rate of adrenalin injection and by the absence of any marked effects from changes of blood pressure, is that the acceleration is wholly or chiefly dependent on the amount of adrenalin delivered in a given time, and is relatively independent of whether the adrenalin is carried in a larger or smaller amount of blood. Of course, if in the reduced animal a notably larger proportion of the blood is caused to pass through the heart than through the rest of the body when the arterial pressure is raised, the amount of adrenalin delivered to the heart in a given time would be increased. As shown by the figures in table 4, however, this does not occur to any noteworthy degree in the reduced animal.

Basing our procedure on the points above mentioned and illustrated, we have compared the increases of heart rate produced by brachial stimulation in a reduced animal with those produced by injecting adrenalin (1:100,000) into the brachial vein. The first row of figures in each of the following illustrative cases presents the initial heart rate for 5 seconds and the reflex increases of rate for 5-second intervals thereafter; the second row (italicised) the corresponding results when adrenalin was injected:

		START	1	2	3	4	5	6	7	8	9
December 11....	10:23	17.0	0	0	1.5	1.5	2.5	3.0	2.5	2.5	2.5
	10:43	*17.5*	*0*	*0*	*1.0*	*2.0*	*2.5*	*2.5*	*3.0*	*2.5*	*2.5*
December 13....	12:10	16.0	0	0	1.5	2.5	2.5	3.0	3.0	2.0	1.5
	12:18	*15.0*	*0*	*0*	*0.5*	*2.0*	*3.0*	*3.0*	*3.0*	*3.0*	*2.5*
December 15....	11:04	20.0	0	1	1.0	1.0	1.5	1.5	1.5	1.0	1.0
	11:08	*21.0*	*0*	*0*	*0*	*1.0*	*1.5*	*1.5*	*1.5*	*1.5*	*1.5*
December 16....	11:07	16.5	0	0	0	1.0	2.5	2.5	3.0	3.0	3.0
	11:15	*17.0*	*0*	*0*	*0.5*	*1.0*	*2.5*	*3.0*	*3.0*	*3.0*	*2.5*

These cases are also included in table 5. The adrenalin injected on December 11 and December 13 was 0.3 cc. in 15 seconds, and on December 16, 0.41 cc. in 20 seconds, i.e., 1.2 cc., 1:100,000, per minute (see fig. 5). Since the weight of the animals varied from 3.2 k. to 3.8 k. in these cases, the rate of reflex adrenal secretion, thus quantitated, would lie between 0.0032 and 0.0037 mgm. per kilo per minute. On December 15, 0.5 cc. was injected in 15 seconds, i.e., 2 cc. per minute;

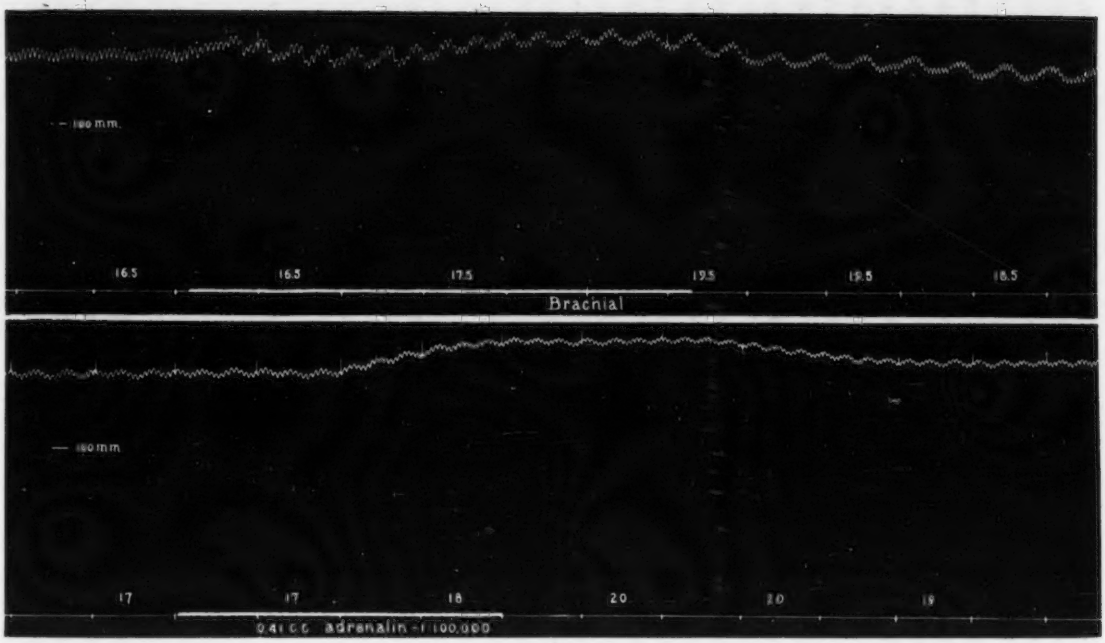

Fig. 5. Records (half-size) showing similar effects of reflex stimulation (brachial, 30 secs., at 11:07) and of adrenalin injection (0.41 cc., 1:100,000, in 20 seconds, at 11:15) on the rate of the denervated heart in a "reduced" animal. See December 16, tables 3 and 5 and p. 333.

since the weight was 4.1 k., the rate of secretion was 0.0049 mgm. per kilo per minute. Using rabbit intestine and uterus segments as means of assaying the adrenin in blood removed from the "cava pocket" in cats, Stewart and Rogoff calculated that the secretion averages 0.00025 mgm. per kilo per minute. This is the persistent, unvarying secretion which they regard as the normal output of the adrenal medulla. We have furnished evidence (see p. 324) that an output approximately twice this amount is being produced under experimental conditions, without special nerve stimulation. The above comparisons of increased pulse rates arising from adrenalin injections and from brachial stimulation, however, show that adrenal secretion can be increased reflexly to a rate more than ten times that which Stewart and Rogoff have set down as the unvarying normal.

SUMMARY

The average increase of rate of the denervated heart, due to splanchnic or reflex stimulation, with the adrenal connections intact, was found to be 29 beats per minute in 104 observations. After removal of the adrenals the average residual increase from the same stimulation was only 6 beats per minute in 163 observations (see table 1). With the adrenals active, therefore, reflex cardiac acceleration is of an order very different from that prevailing after the glands have been excised.

The residual increase of heart rate after removal of the adrenals was proved to be not due to a rise of arterial pressure, whether the rise started from a low or high initial level, or whether it was abrupt or gradual, or whether the duration of the higher pressure was short or long (see table 2).

The increased rate after adrenalectomy could not be explained by changes of venous pressure, nor by improvement of a poor circulation, nor by warmer blood coming to the heart, nor by the activity of accessory adrenal tissue.

The residual reflex acceleration of the heart after adrenalectomy disappeared when the hepatic nerves were cut—we did not see the rate increase more than two beats per minute after exclusion of the adrenals and the liver. This acceleration is, therefore, due to a factor or to factors hitherto unknown.

We have pointed out that Stewart and Rogoff's quantitative method is superposed on unproved assumptions that their procedure, which fails to reveal reflex adrenal secretion, is correct, and that the various procedures of other investigators, which yield positive evidence of reflex

adrenal secretion, can be accounted for by a "redistribution of blood in the body."

By use of a "reduced" animal (i.e., one with both carotid, both brachial and both renal arteries tied, the aorta closed below the renals, and the mesenteric nerves cut) vascular reflexes were reduced to a minimum, the liver was excluded, and the adrenals were the only abdominal viscera left innervated. Typical reflex accelerations of the heart (averaging 26 beats per minute) occurred in this preparation, although the changes of blood pressure were insignificant or were only moderate variations either up or down (see table 3 and figs. 1 and 5). Under these circumstances, the more rapid beat cannot be attributed to a "redistribution of blood in the body," for the possibilities of redistribution were lacking.

The adrenal glands were removed, the hepatic nerves cut, and adrenalin at the rate of approximately 0.0007 mgm. per kilo per minute was injected by vein, continuously, to replace the continuous, unvarying adrenal secretion assumed by Stewart and Rogoff, on the basis of their eye test, to be normal. This amount restored the pulse to the rate which prevailed before adrenalectomy (see fig. 2), and therefore represents the constant secretion of adrenin under experimental conditions. It is more than twice the amount found by Stewart and Rogoff when blood was assayed outside the body and, as they admit, adrenin thereby "lost." We have called attention to their two standards of adrenal secretion, the internal and the external, and to pertinent questions which should be considered in relation to them.

After the heart rate was restored by constant injection of adrenalin, typical reflex vascular responses were induced by afferent stimulation, but either no acceleration of the pulse occurred or an insignificant increase of 2 beats per minute (see table 4 and fig. 2). Again the evidence is clear that the faster rate is not due to "redistribution of blood in the body."

We have pointed out that since the denervated heart is insensitive to all except chemical agents delivered through the blood stream, the striking cardiac acceleration which follows afferent stimulation when the adrenals are the only responsive abdominal viscera, and the absence of this reflex acceleration when thereafter the adrenals are removed, can be explained only by the action of secreted adrenin reflexly increased and carried to the heart in the circulation.

The denervated heart in the "reduced" animal was found to be a means of assaying adrenin. Repeated equal doses injected intravenously at a uniform rate repeatedly produced in a given animal the

same or nearly the same maximal increases of heart beat, and if the injections differed in rate, the increases likewise differed in degree (see table 5 and fig. 4). With the circulation simplified, as in the reduced animal, the acceleration is chiefly or wholly dependent on the rate of injection, and is little, if at all, influenced by variations in blood pressure.

By matching adrenalin injections with reflex adrenal secretion (see fig. 5) we have shown that when the heart rate is accelerated between 30 and 42 beats per minute, the output from the adrenal glands lies between 0.0032 and 0.0037 mgm. adrenin per kilo per minute, i.e., more than ten times the amount found by tests made outside the body and regarded by Stewart and Rogoff as the unvarying normal secretion.

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

VII. The Reflex Center for Adrenal Secretion and Its Response to Excitatory and Inhibitory Influences

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In the preceding paper of this series (1) data were reported confirming earlier evidence from this laboratory that the adrenal medulla is subject to reflex stimulation. Two interesting questions arise regarding the nervous control of adrenal secretion: *a*, Where is the reflex center located? *b*, Can the secretion be inhibited, and, if so, is the mechanism central or peripheral? These two questions we propose to consider.

The location of the reflex center for adrenal secretion. There is general admission that the secretory fibers for the adrenals run in the splanchnic strands. According to Langley, the splanchnics in the cat receive contributions through the white rami from the fourth or fifth thoracic to the second lumbar nerves (2). Obviously, direct stimulation of the spinal cord within this range would occasion discharge of nerve impulses to the splanchnics and thereby induce an output from the adrenals. Stewart and Rogoff state: "The only way in which we have hitherto been able to bring about an unequivocal increase in epinephrin output (apart, of course, from that due to stimulation of the peripheral end of the splanchnic nerve) is by the administration of strychnine or the intravenous injection of small quantities of concentrated salts (sodium carbonate), which cause an excitation of the spinal cord" (3). According to these authors, the center associated with the constant unvarying adrenal secretion observed by them is located in the upper part of the thoracic cord (4). They found that neither this center nor any other part of the central nervous system could be stimulated reflexly to produce an increased output from the adrenals (5). Recently, however, we have observed that adrenal secretion can be evoked reflexly in an amount more than ten times that

estimated by Stewart and Rogoff as the unvarying output of the glands. The normally secreted substance we assayed by use of the denervated heart in a "reduced" animal (1). In the present investigation we have again relied on this indicator of adrenal secretion, usually with the animal under ether anesthesia, but occasionally under urethane. In our earlier experiments the larger arteries were not tied nor were the mesenteric nerves cut. Objection might be raised to this preparation because of the possibility that with it the denervated heart may be accelerated, even though the adrenal glands have already been removed. As was shown in the preceding paper, however, in only 6 per cent of cases of adrenalectomy is the increase more than fifteen beats a minute. So long as larger increases than these are obtained repeatedly, there is little reason for suspecting that any other factor than increased adrenal secretion is playing a dominant rôle in making the heart beat faster. Furthermore, as will be shown, we have confirmed our earlier experiments by obtaining similar results when the adrenal glands were the only innervated abdominal viscera.

That reflex adrenal secretion is not mediated through the basal ganglia was proved by obtaining a typically faster beat of the denervated heart after the brain stem in front of the corpora quadrigemina had been cut across. Following are some records of increased rate per minute under these circumstances, when the sciatic or brachial was stimulated.

DATE	STIMULATION	HEART RATE		
		Before	After stimulation	Increase
March 3	Sciatic	224	242	18
March 8	Sciatic	192	210	18
March 8	Sciatic	180	208	28
	Sciatic	184	212	28
March 12	Sciatic	212	236	24
March 15	Sciatic	152	192	40
March 17	Brachial	184	210	26
March 19	Brachial	236	268	32
March 31	Brachial	216	228	12

Transection of the brain stem may be accompanied by a large increase of heart rate. In the experiment of March 12, for example, severance of the stem in front of the colliculi occasioned a transient increase from 202 to 236 beats per minute. See also table 2, March 31.

On two occasions after removal of the cerebrum the cerebellum was carefully excised and reflex stimulation tried. Accelerations of the heart occurred in both experiments. The cerebellum is clearly not essential to reflex secretion of adrenin.

In securing further evidence as to the location of the reflex center, great care had to be exercised to avoid injury of parts near those being tested. The procedure which finally proved most satisfactory was that of removing the front of the cerebrum with a Sherrington decerebrator, leaving parts of the occipital lobes and basal ganglia. Now, with a sharp, thin-bladed knife the occipital lobes were excised (after clipping off more of the skull, if necessary) and a transection was made just in front of the corpora quadrigemina. Access to the region immediately back of these bodies requires the removal of the bony tentorium that lies over them. In order to avoid injury to the nervous structures close by, this must be done with extreme care.

We soon found that it was possible to exclude the anterior colliculi and still obtain satisfactory reflex responses. On March 31, for example, brachial stimulation caused an increase of 18 beats per minute after isolation of the anterior colliculi—6 beats more than the increase which had occurred earlier when the transection was in front of these bodies. Obviously the center does not lie in that region.

When we tried to secure reflexes after transecting immediately behind the corpora quadrigemina we encountered repeated failures. Reflex effects which again and again had been secured before that step was taken failed after it was taken. It was clear that the center was either in the posterior colliculi or close to the line of transection in the floor of the fourth ventricle. Finally, by use of an especially sharp knife, we were able to excise the corpora and still obtain reflex acceleration (16 beats per minute, see fig. 1). This was on March 31 when, as stated above, the acceleration after removal of the anterior colliculi was 18 beats per minute. After this success a cut across the stem only 2 mm. farther back promptly and completely abolished the reflex. These observations place the center immediately back of the corpora quadrigemina in the floor of the fourth ventricle.

In 1912, Elliott reported reflex exhaustion of the adrenal after severance of the brain stem just in front of the corpora quadrigemina. He drew the conclusion that the reflex center lay not higher than the corpora, and inferred that it was apparently "associated with the nervous machinery in the neighborhood of the vasomotor center which governs other sympathetic emotional musculature" (6). A similar inference

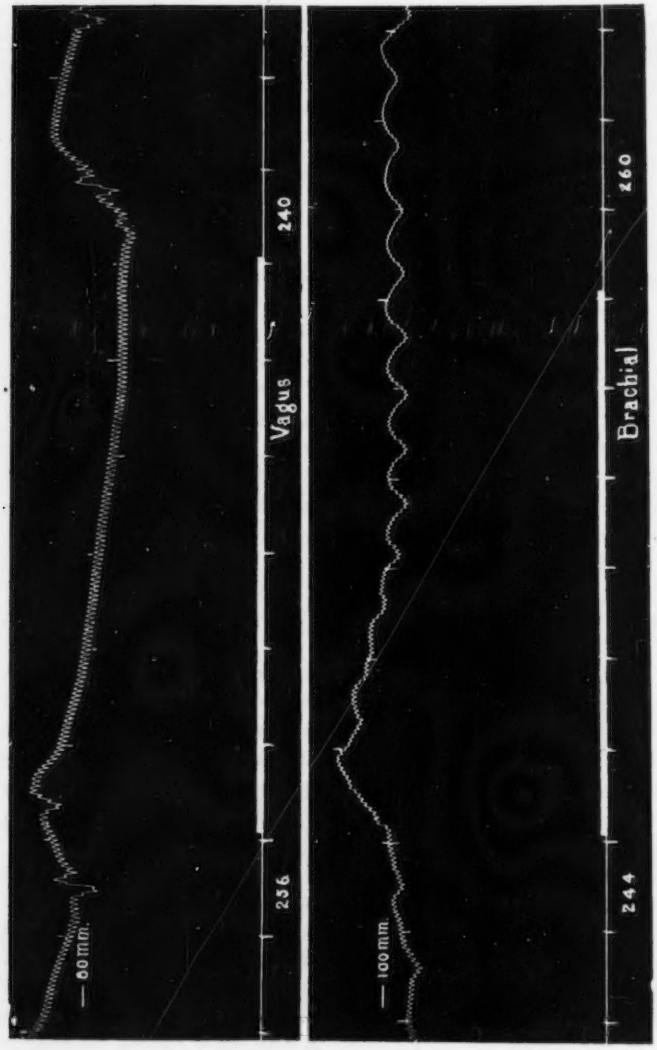

Fig. 1. Records taken after excision of corpora quadrigemina (at 3:15). Slowing of the denervated heart (16 beats per minute) by central vagus stimulation (at 3:17). Acceleration (16 beats per minute) by brachial stimulation (at 3:24). Here and in other records, time, 5 seconds; time-line, zero pressure.

was drawn by Anrep in 1912 (7). The evidence offered in our results is confirmatory of Elliott's and Anrep's suggestions.

INHIBITORY CONTROL OF ADRENAL SECRETION. A question of considerable interest in relation to endosecretory glands is the mode of checking their activity. Is there a double nerve supply as, for example, in the salivary glands, or is there a single nerve supply from the medullary center with excitatory and inhibitory influences playing upon it?

In order to study the action of inhibitory nerves, it must first be proved that there is a constant secretion from the adrenals which is maintaining the cardiac rate at a higher level than would be maintained were the glands removed. Evidence on this point has already been given in an earlier paper (8). Stewart and Rogoff have questioned whether the slower rate of the denervated heart after removal of the adrenal glands may not be due to a fall of blood pressure following the operation (9). In table 1, however, are presented the blood pressures and rates of beat of the denervated heart before and after adrenalectomy in a series of animals in which the operation was not attended by any noteworthy fall of blood pressure. As inspection of the table shows, a decrease in cardiac rate is always present and considerable. The testimony of these experiments, therefore, is confirmatory of Stewart and Rogoff's conclusion that under experimental conditions there is a continuous output of adrenin without special stimulation of the splanchnics, either directly or reflexly.

In an earlier paper attention was called to an occasional *decrease* instead of increase in the rate of the denervated heart following sciatic stimulation (8, p. 417). Instances were given of reduction of rate varying from 4 to 20 beats per minute. These changes were not associated with important alterations of blood pressure. It seemed possible, therefore, that there were depressor influences which might arise from stimulation of peripheral nerves.

Whether depressor influences might be exerted centrally or through another nerve path than the splanchnics was considered some years ago in making tests on the electrical response accompanying stimulation of the adrenals. The only nerve belonging to the cranial division of the autonomic system that could possibly act antagonistically to the splanchnics is the vagus. It was found, however, that when the peripheral end of the vagus was stimulated in the lower thorax no change was recorded in the galvanometer. Correspondingly we have noted that stimulation of the peripheral end of the cut vagus in this region does not

TABLE 1

Decrease of rate of the denervated heart after removal of the adrenal glands without noteworthy fall of blood pressure

DATE	TIME	HEART RATE PER MINUTE		BLOOD PRESSURE	
		Before adrenalectomy	After	Before adrenalectomy	After
				mm. Hg.	*mm.* Hg.
October 7	10:44	176		106	
	10:52	184		108	
	10:55	180		108	
	11:25		162		106
November 18	10:21	219		96	
	10:43		168		104
December 24	10:35	182		148	
	10:40	182		148	
	11:09		160		148
	11:14		166		153
	11:19		168		146
	11:24		164		144
December 29	10:34	224		141	
	11:00	216		116	
	11:20		182		103
	11:25		172		118
January 5	11:30	174		135	
	11:33	174		145	
	11:36	174		160	
	11:44	168		142	
	12:06		150		145
	12:11		144		142
January 12	9:42	128		172	
	9:48	132		162	
	10:16		116		160
	10:22		115		152
	10:34		117		162
January 15	10:06	214		162	
	10:11	200		154	
	10:32		182		156
	10:37		176		166
	10:43		176		166
	10:51		176		166
	11:07		174		164

influence the rate of the denervated heart. From these observations it would appear that the probable mode of checking adrenal secretion is through inhibitory influences brought to bear on the medullary center.

An afferent nerve having an action which, in relation to arterial pressure and heart rate, would be synergistic with checking of adrenal secretion is the depressor. Richards and Wood have reported finding a less amount of adrenin in blood collected from the adrenal veins, when taken during stimulation of the depressor nerve and tested by means of isolated intestinal muscle (10). On the other hand, Gley and

TABLE 2

Slowing of the denervated heart due to central stimulation of the cut vagus or depressor nerve.

DATE	TIME	NERVE	HEART BEATS PER MINUTE		
			Before stimulation	Just after	Decrease
March 31	2:33	Vagus	214	200	14
	2:42	Vagus	224	206	18
	3:15	(Corp. quad. out)			
	3:17	Vagus	256	240	16
	3:27	Vagus	264	248	16
April 2	3:03	Depressor	260	248	12
	3:38	Vagus	248	242	6
	4:13	Vagus	268	258	10
April 6	3:19	Vagus	212	192	20
	3:43	Vagus	192	168	24
	3:58	Vagus	180	168	12
	4:08	Vagus	190	172	18
	4:28	(Adrenals out)			
	4:34	Vagus	160	158	2

Quinquaud state that depressor stimulation in the rabbit does not lessen the amount of the adrenin in blood from the adrenal vein (11). Evidently further evidence is desirable. Our experiments we have based on the fact illustrated in table 1, that if the discharge of adrenin into the circulating blood is diminished, the rate of the denervated heart is likewise diminished. This preparation, therefore, can be employed as a means of determining whether stimulation of the depressor nerve or of afferent depressor fibers in the cut vagus trunk will have an inhibitory effect on adrenal secretion.

When in an animal with the heart isolated from the central nervous system the central end of the cut vagus nerve is stimulated, a slowing of the rate is recorded. The amount of slowing may be considerable. In our experience the rate has been reduced between 4 and 24 beats a minute. These effects have been obtained not only by stimulating the main vagus trunk, but also by stimulating the depressor strand occasionally separate in the cat.

Such reflex decreases of rate can be obtained after removal of the cerebrum and also after sectioning the brain stem either between the anterior and posterior colliculi or immediately behind those bodies. (See fig. 1 and table 2.) The cut which abolished the augmentor reflex March 31 also abolished the depressor reflex.

The time between the start of stimulation and the first 5-second period thereafter in which a change of heart rate occurred was longer for vagal decrease than for brachial increase. The following figures, giving the increase and decrease of beats in 5-second periods from the start of stimulation, are illustrative of this point:

DATE	TIME	STIMULATION	1	2	3	4	5	6	7	8	9
April 7...	3:35	Brachial increase	0	0.5	0.5	1	2	2.5	2.5	3	3
	3:40	Vagal decrease	0	0	0	0	1	1.5	1.5	2	2
March 31.	3:07	Brachial increase	0	0	0.5	1	2	2			
	2:42	Vagal decrease	0	0	0	0	0.5	0.5	1.5	1.5	1.5
	3:24	Brachial increase	0	0	0.5	1	1	1	1.5	1	
	3:17	Vagal decrease	0	0	0	0	0.5	1	1	1	
May 25 ..	11:29	Brachial increase	0	0	1	2	2	2.5	3	2.5	
	11:05	Vagal decrease	0	0	0.5	1	1.5	1.5	1.5	1.5	

Not only was vagal stimulation slower than brachial stimulation in starting a change of rate, but vagal stimulation was usually more lasting in its effect. Whereas the brachial increase commonly begins to subside 10 or 15 seconds after a half-minute stimulation has ceased, the vagal decrease has been observed to continue as long as 110 seconds.

If rhythmically repeated afferent stimulation of the brachial or sciatic nerve is maintaining the heart rate at a higher level by reflex adrenal discharge, the application of a stimulus to the central end of the vagus will soon cause diminution of the rate. In figure 2 are shown the effects of inhibiting through the vagus the reflex center for adrenal secretion that was being stimulated to extra activity by repeatedly tet-

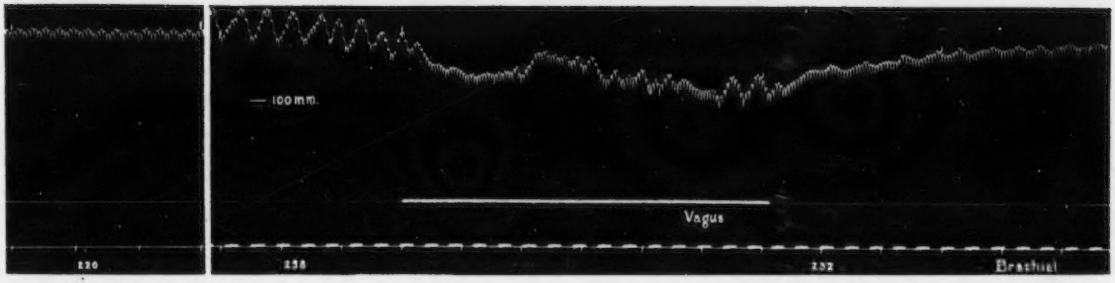

Fig. 2. First portion at 3:49, before stimulation (rate of denervated heart, 220 beats per minute). Second portion, at 3:50, starting after repeated tetanizing current had been applied to the brachial for 25 seconds. Rate of denervated heart thus raised to 258 per minute (38 beats). Central vagus stimulation reduced the rate to 232 per minute (26 beats).

TABLE 3

Effects on the rate of the denervated heart of stimulating for 30 seconds the central end of the cut vagus, the brachial, or the two nerves simultaneously.

DATE	TIME	NERVE	HEART BEATS PER MINUTE			
			Before stimulation	Just after	Increase	Decrease
April 8	2:22	Vagus	206	194		12
	2:34	Brachial	192	213	21	
	2:43	Vagus	200	192		8
	2:48	Brachial	208	228	20	
	2:55	Vagus + Brachial	208	198		10
	3:02	Brachial	220	238	18	
	3:33	(Adrenals out)				
	3:36	Brachial	194	198	4	
	3:38	Brachial	196	200	4	
	3:44	Vagus	198	194		4
	3:50	Vagus	200	198		2
	3:55	Vagus + Brachial	196	196	0	0
	3:59	Brachial	196	198	2	
April 16	2:53	Brachial	162	183	21	
	3:00	Vagus + Brachial	164	164	0	0
	3:07	Brachial	168	183	15	
	3:54	Vagus + Splanchnic	183	222	39	
May 4		Brachial + Vagus	224	216		8
	4:30	Brachial	228	256	28	
		Brachial + Vagus	256	242		14
	4:45	Vagus	216	208		8
	4:56	Brachial	220	234	14	
May 24	11:30	Brachial	208	244	36	
	11:33	Vagus	208	196		12
	11:58	(Animal "reduced")				
	12:01	Brachial	212	238	26	
	12:07	Vagus	202	192		10
	12:21	Brachial + Vagus	212	222	10	
	12:29	Brachial + Vagus	216	210		4
	12:44	Brachial	220	236	16	
	12:49	Vagus	220	208		12

TABLE 3—*Concluded*

DATE	TIME	NERVE	HEART BEATS PER MINUTE			
			Before stimulation	Just after	Increase	Decrease
May 25	10:58	Brachial	228	242	14	
	11:05	Vagus	236	216		20
	11:25	(Animal "reduced")				
	11:29	Brachial	210	234	24	
	11:33	Vagus	216	198		18
	11:37	Brachial	212	232	30	
	12:00	Vagus	200	188		12

anizing the brachial nerve. The heart rate, which had been increased 38 beats by the latter stimulation, was reduced 26 beats when the vagus was stimulated; and after vagus stimulation ceased the rate increased again, though only to a slight degree (4 beats per minute.) Repeated tetanizing of the brachial alone for 5 minutes resulted in an increase of rate with no drop such as that shown in figure 2; that result, therefore, is not a fatigue effect. In table 3 are presented some results on the rate of the denervated heart of brachial stimulation alone, vagus stimulation alone, and simultaneous stimulation of both the excitatory and the inhibitory nerves.

As was shown in figures 1 and 2, vagus stimulation is accompanied both by a cessation of respiration and by a fall of blood pressure. Elsewhere we have summarized the evidence that changes of blood pressure have insignificant effects on the heart rate (1). A prolonged low pressure will doubtless decrease the number of beats per minute, but in our experience a fall of arterial pressure due to partial closure of the inferior vena cava does not induce in 25 or 30 seconds a decrease in the heart rate of more than 4 beats per minute. A reflex lessening of the number of beats by 16, 18 and 24 per minute, occurring at the end of 30 seconds' stimulation, such as we have recorded, cannot be accounted for by the reduced pressure. Nor does stoppage of respiration explain the slower beat, for, as previously shown, the primary effect of asphyxia when the adrenals are present is to make the heart beat faster (8). Furthermore, as shown in figure 3, excision of the adrenals practically abolishes the reflex slowing of the heart. In that instance, stimulation of the vagus had earlier (at 3:43, see table 2, April 6) caused a fall of 24 beats per minute; at 4:08 the reduction was 18 beats. The adrenal glands were then removed (4:28). Vagus stimulation (at 4:34) after

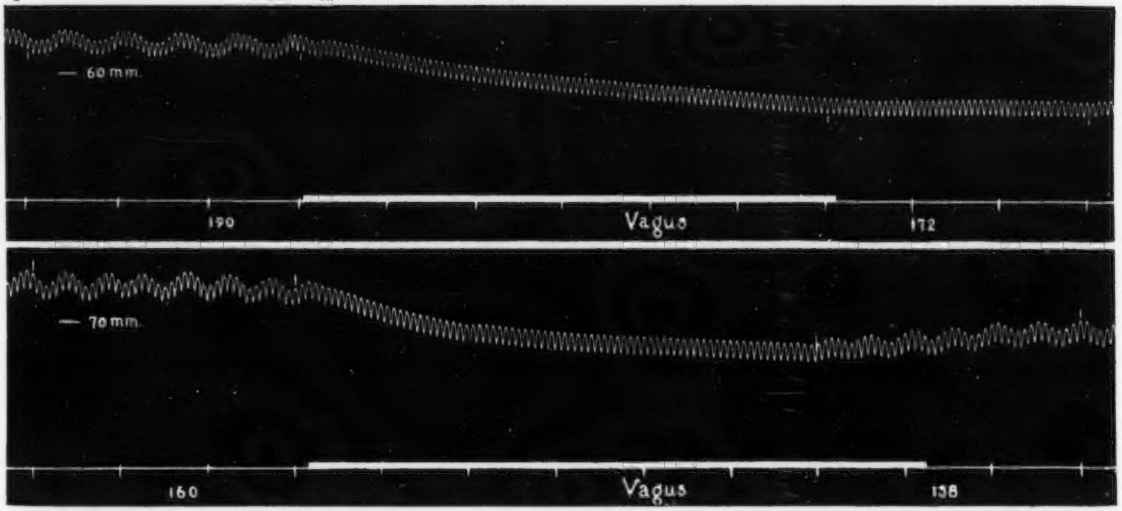

Fig. 3. Upper record, at 4:08, central vagus stimulation, 30 seconds; the rate of the denervated heart reduced from 190 to 172 beats per minute, 18 beats. Adrenalectomy completed at 4:28. Lower record, at 4:34 central vagus stimulation, 35 seconds; the rate reduced from 160 to 158, 2 beats.

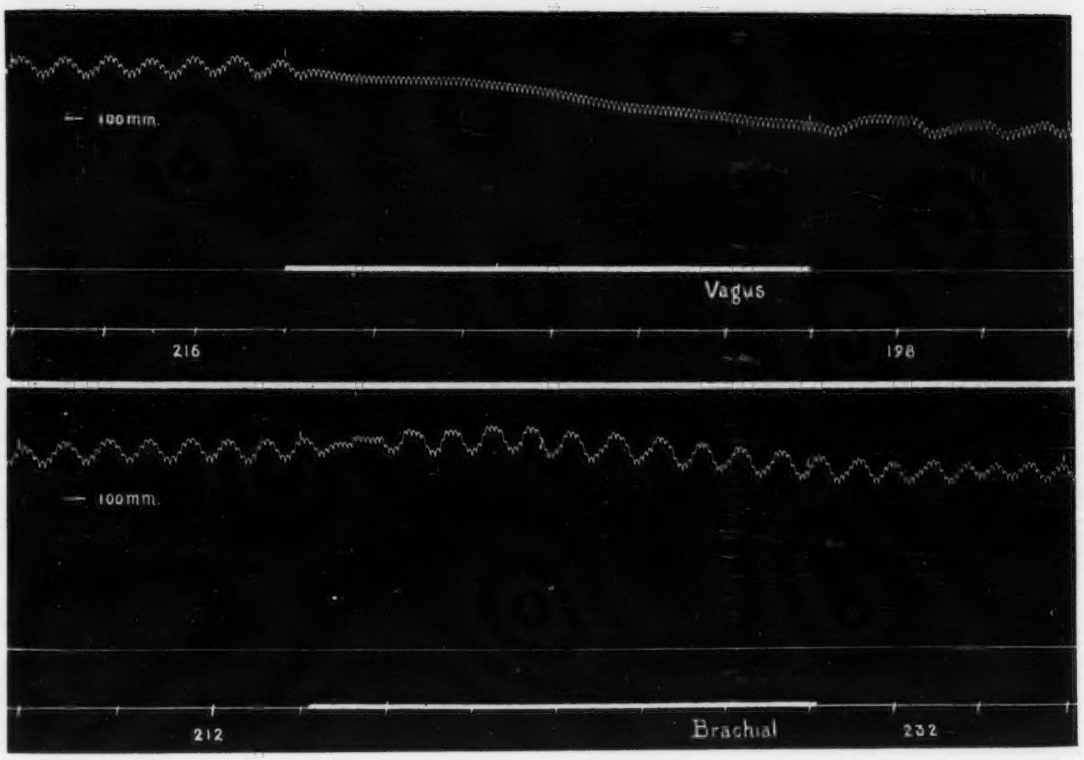

Fig. 4. Records taken from a "reduced" animal (i.e., with renal arteries, aorta and inferior cava below renal vessels, carotids and subclavians tied, and all mesenteric nerves cut). Upper tracing, at 11:33, afferent vagus stimulation, 30 seconds; rate of the denervated heart reduced from 216 to 198 (18 beats) per minute. Lower tracing, at 11:37, brachial stimulation, 30 seconds, the rate increased 212 to 232 (20 beats) per minute.

their removal, though lowering the blood pressure as before and causing a suspension of respiration, reduced the rate only 2 beats.

Proof that the effects of afferent stimulation are not dependent upon redistribution of blood in the body is offered in table 3 and in figure 4. The records represented in that figure were obtained in a "reduced" animal, i.e., in an animal with both carotids, both subclavians, the renal arteries, the inferior cava and the aorta below the renals all tied and the mesenteric nerves cut. Typical changes in heart rate occurred, though the vessels under nervous control were only those of the thoracic and upper abdominal wall.

If the action of the depressor nerve consists in a paralysis of the splanchnics, there should be produced in consequence of depressor stimulation a diminished adrenal secretion, according to Gley and Quinquaud, for under these conditions the splanchnics, as secretory nerves of the adrenals, would suffer a diminution of all their functions. Failure to find any lessening of adrenal output in consequence of depressor stimulation they have interpreted as a new argument in favor of the view that the depressor acts not by lessening vasoconstrictor tone, but by exciting vasodilator centers. The evidence presented in the foregoing pages confirms the work of Richards and Wood rather than that of Gley and Quinquaud, i.e., it shows that there can be inhibition of adrenal secretion either by stimulation of the depressor itself, or by stimulation of depressor fibers in the vagus. And since continuous adrenal secretion is dependent on the integrity of splanchnic pathways (12), the inhibition is doubtless exercised through an effect on the tonic activity of the splanchnic center in the medulla.

SUMMARY

Reflex acceleration of the denervated heart can be evoked after removal of the cerebrum and the corpora quadrigemina. A transection a few millimeters back of these bodies destroys the reflex.

Removal of the adrenal glands without a fall of blood pressure lessens the rate of the denervated heart. Under experimental conditions, therefore, a continuous adrenal discharge is going on. On this fact as a basis a slowing of the heart rate in consequence of stimulation has been regarded as due to diminished adrenal secretion.

Stimulation of the central end of the vagus or of the depressor nerve in the cat will cause the denervated heart to beat more slowly by as much as 24 beats per minute. This occurs even though the corpora

quadrigemina and all parts anterior to them have been removed. It disappears when the brain stem is severed a few millimeters back of the corpora.

Reflex inhibition of the heart disappears when the adrenal glands are excised.

Augmentor and depressor action on the center are directly antagonistic. If reflex adrenal secretion is maintaining the denervated heart at a faster rate, central vagus stimulation will greatly diminish the rate.

The antagonism between vagus and brachial effects occurs in an animal with its controlled circulation reduced to a minimum; they are therefore not dependent upon a redistribution of blood in the body.

We conclude that the reflex center for adrenal secretion is located near the upper or front edge of the floor of the fourth ventricle, and that it is subject to both excitatory and inhibitory nervous influences.

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

VIII. Some Effects on the Denervated Heart of Stimulating the Nerves of the Liver

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In 1920 Stewart and Rogoff called attention to the fact that after removal of the adrenal glands, splanchnic stimulation causes a faster rate of the denervated heart (1). This acceleration they attributed chiefly to the rise of arterial pressure which accompanies the stimulation, though they referred to variations of venous flow into the heart and "increased mobilization of sugar or other changes in the liver through the splanchnics" as possible accessory factors in producing the change. Further than this they did not go, declaring that explanation of the mechanism of the response was not their concern. In a previous paper of this series, evidence has been presented proving that the residual increase of heart rate after adrenalectomy is not due to rise of arterial pressure, nor to changes of venous pressure nor to improvement of a poor circulation, nor to warmer blood coming to the heart from the abdominal organs, nor to the activity of accessory adrenal tissue (2). Nevertheless, as Stewart and Rogoff's observations and as similar observations made in this laboratory have shown, splanchnic stimulation after removal of the adrenals may cause the heart rate to increase more than 35 or 40 beats per minute, though usually the acceleration does not reach nearly that degree. In consideration of the remarkable steadiness and uniformity of the heart rate in the presence of the factors mentioned above, it is clear that there must be some other hitherto unknown factor at work causing the faster rate, and that this factor, since called forth by splanchnic stimulation, has its origin in the abdomen. We were interested to know under what circumstances it could be set in operation. In our experiments cats were used and were kept under ether anesthesia as uniformly as possible

throughout the procedure, and at the end were killed by over-etherization.

THE HEPATIC ORIGIN OF THE FACTOR ACCELERATING THE DENERVATED HEART. The first step toward discovering the agency which, after removal of the adrenals, causes the denervated heart to beat more rapidly was taken by stimulating the splanchnics while the inferior vena cava was closed immediately below the liver. On January 7, at 10:54, splanchnic stimulation for 30 seconds caused the heart rate to rise from 144 to 162 beats per minute—18 beats. At 11:05 a looped thread which had been placed as far forward as possible around the abdominal cava and passed out through a small glass tube, was pulled upon while the tube was pressed inward. Thus the cava was closed. During the period of closure, exactly the same splanchnic stimulation as before caused again an increase of 18 beats. This experiment has been confirmed in other cases. The results thus obtained prove that the factor does not come from the kidneys or from the back wall and that its origin therefore must be in some part of the splanchnic area drained through the portal or the hepatic veins.

In further tracing the accelerating factor, the splanchnic was stimulated while the portal vein was closed at its entrance into the liver. The method of closure was that used on the inferior cava. On January 7, at 12:05, stimulation for 30 seconds increased the rate from 156 to 162 beats per minute—6 beats. Five minutes later, while the portal vein was closed, the same stimulation raised the rate from 152 to 158, again an increase of 6 beats. In other similar experiments the usual increase of rate occurred, although the portal was closed. As will be shown in a later paper, however, there may be some lessening of the increase under these circumstances, but not a total disappearance of it. The foregoing evidence indicates that the factor accelerating the denervated heart after adrenalectomy neither rises from the kidneys nor from the back wall nor from any other abdominal organ—stomach, intestines, spleen or pancreas—except the liver.

If both the hepatic artery and the portal vein are closed the effect of hepatic nerve stimulation is greatly reduced or abolished. For example, on January 7, at 11:05, though closure of the cava permitted hepatic stimulation to raise the heart rate by 18 beats per minute, after closure of both hepatic vessels the same stimulation (11:12) increased the rate by only 4 beats. And on March 5, stimulation of the hepatic nerves (at 11:06) with the artery and vein closed had no effect on the heart, whereas before (at 10:53) the acceleration was 32 beats per minute, and afterwards (at 11:14) it was 10 beats, and at 11:25,

30 beats. The activity of the factor when blood is flowing through the liver alone, and the diminution or absence of effect when the hepatic circulation is stopped points clearly to the liver as the source.

Massage of the liver will itself induce a faster heart rate. On different occasions we have observed increments varying from 3 to 14 beats per minute following repeated gentle pressure of the liver lobes between finger and thumb. Once we obtained no increase by this procedure. The positive effect, however, coincides with the other testimony that the accelerating factor has an hepatic origin.

That the liver is the source of the accelerating factor was further confirmed in a series of experiments in which, with the adrenals excised, the splanchnic was stimulated before and after the severance of the hepatic nerves. The results of these experiments were presented in an earlier paper of this series (2, p. 318). It was there shown that whereas before the hepatic nerves were cut splanchnic stimulation caused increases of rate varying from 4 to 10 per minute, after the cutting the same stimulation caused either no increase whatever, or an increase of only 2 beats per minute. We do not think that this slight acceleration should modify the conclusion that the accelerating factor arises in the liver.

Because peripheral splanchnic stimulation, in the absence of the adrenal glands, makes the denervated heart beat faster, though the inferior cava and portal veins are closed, and because this effect wholly or nearly disappears when both the hepatic artery and the portal vein are closed or when the hepatic nerves are cut, we conclude that the agent increasing the cardiac rate is a substance given off into the blood stream by the liver.

EFFECTS OF STIMULATING THE HEPATIC NERVES. Since the foregoing tests point to the liver as the origin of the accelerating factor, it should be possible to increase the rate of the denervated heart by stimulating the hepatic nerves direct. In our first experiments, the nerves were isolated on the hepatic artery distal to the gastroduodenal branch. Soon evidence was obtained that stimulation of the nerves accompanying this branch was without effect on the heart rate. Consequently, the electrodes were thereafter applied to the nerve filaments isolated from the hepatic artery proximal to the gastroduodenal branch, at a region where they could be conveniently reached. The filaments were invariably tied and cut. In many of the experiments, shielded electrodes were employed and the abdominal cavity kept continuously closed after they were set in place. Almost without exception the adrenals were removed before stimulation was started.

Acceleration of the denervated heart. In table 1 are presented effects on the cardiac rate of stimulating the hepatic nerves in a series of 24 animals. The stimulation was invariably for 30 seconds and was strong because accompanying the nerve filaments were other tissues which shared the current. The table reveals a wide variation in the increment of rate; always there was some increment, and in only one case was it as low as 2 beats per minute. Usually the minimal increase was 4 beats. In a former series of observations, 25 instances were reported in which no increase of rate whatever was observed after adrenalectomy (3). Those were the results of attempts at securing *reflex* effects, however, and not the effects of direct stimulation of the hepatic nerves.

TABLE 1

Acceleration of the denervated heart induced by stimulating the hepatic nerves

ANIMALS FASTING					ANIMALS DIGESTING MEAT					
January 14	4	3			January 11*	6	8			
January 21	6				January 13*	10	4			
January 22	4	4	3	3	January 15	10	12	10	8	6
January 27	4	8			January 18	46	36	30	10	
February 5	2				January 19	12	12	6		
February 18	6	4			January 20	18	18	6	16	
February 19	7	10			February 17	20	16	30		
February 21	9				April 5	12	14			
February 26	5				April 6	16	14	16		
February 28	8				April 8	26	12	22		
March 2	2				April 12	26	12	8	10	
March 4	6	4			April 14	22	18	12		
March 7	6	6								

* Digestion started, not advanced.

In the first two columns below are given figures showing the range of distribution of the increments of cardiac rate after hepatic stimulation as observed in the present series:

INCREASE OF HEART BEATS PER MINUTE	NUMBER OF CASES	NUMBER OF CASES (REFLEX AND SPLANCHNIC STIMULATION ADRENALS OUT)
1- 5	13	22
6-10	22	30
11-15	9	11
16-20	8	4
21-25	2	3
26-35	4	5
36-45	1	3
46-55	1	

Comparison of this distribution of cases with that in the third column, which presents Stewart and Rogoff's cases of faster cardiac beat from splanchnic and sciatic stimulation after adrenalectomy (1), shows a sufficiently close correspondence to permit placing this with the other evidence that the increment which they observed was due to stimulation of the liver.

After stimulation of the hepatic nerves, the heart rate does not show any marked change for about 15 seconds. Thereafter, the rate rapidly rises and when the period of stimulation lasts for 30 seconds the rate reaches its maximum at the end of about 45 seconds from the start. Following the maximum, there is a slow decline of the rate. In figure 1 are shown the average increments of heart beats in 5-second intervals in 5 cases of hepatic stimulation and also the increments resulting from reflex stimulation of the adrenals in 5 "reduced" animals, i.e., animals with the main arterial trunks tied and the mesenteric nerves cut, thus eliminating involvement of the liver. The figure brings out clearly the fact that the adrenal effect is more prompt in appearing and subsides more rapidly than the hepatic effect.[1]

Rise of blood pressure. Accompanying the stimulation of the hepatic nerves there is an increase of blood pressure starting usually within a few seconds after the stimulus is applied and, when the stimulation lasts 30 seconds, rising to a maximum 45 or 50 seconds after the start. As shown in figure 2, the rise differs from that which is seen when, in the same animal, the splanchnic is stimulated after severance of the mesenteric nerves, and thus adrenal secretion is allowed to act under the same conditions as the agent from the liver. The rise of pressure is uniform in the case of hepatic stimulation. On the other hand, adrenal stimulation is accompanied by a primary sharp rise of pressure with a secondary hump and a later marked dip before the second higher and more prolonged rise occurs. This is the typical blood-pressure curve resulting from splanchnic stimulation, as described by Pearlman and Vincent (4).

[1] A curious effect noted in one instance was a doubling of the heart rate on stimulating the hepatic plexus. The heart (March 2) was beating at the rate of 133 beats per minute. At 3:21 hepatic stimulation increased the rate to 135 per minute. At 3:26 the rate had doubled, i.e., it was 256 per minute. At 4 o'clock, the rate fell again to 126 and on stimulating the hepatic fibers, it changed from 126 to 254. The same doubling of rate occurred at 4:16 as a consequence of stimulation. The animal apparently had a condition of heart block which was removed by excitation of the hepatic nerves.

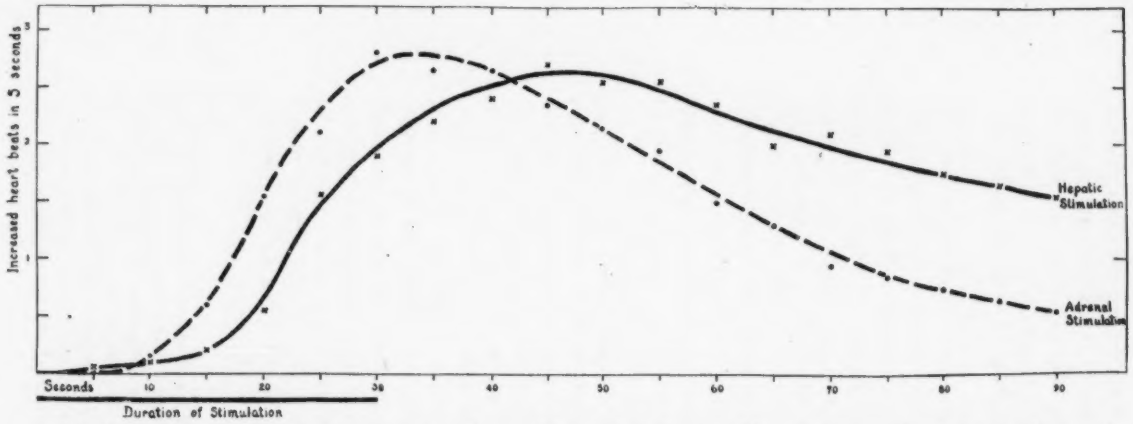

Fig. 1. Average increments of heart rate in 5-second intervals in 5 cases of hepatic-nerve stimulation for 30 seconds (continuous line); and average increments of rate in the same intervals from reflex adrenal stimulation in 5 "reduced" animals (dash line).

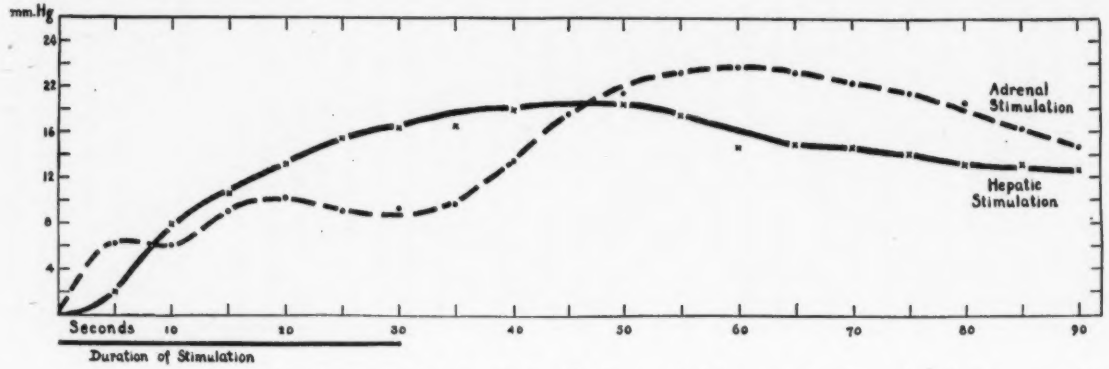

Fig. 2. Increases of blood pressure in an animal with all mesenteric nerves cut. Long-dash line, average of 4 results of hepatic-nerve stimulation, short-dash line, average of 9 results of splanchnic (i.e., adrenal) stimulation.

It might be argued that the rise of blood pressure following hepatic stimulation is due, not to any material contributed to the blood stream from the liver but to a closure of the hepatic vessels so that the splanchnic area is blocked and the pressure rises in consequence of it. Several considerations lead to the inference that this explanation does not account for the rise of pressure. First, the mechanical closure of the portal vein is not associated with a rise of pressure, nor is closure of the hepatic artery. If both are occluded simultaneously, there may be no rise, or there may be a momentary slight rise, followed in the course of a minute by a fall below the original pressure. According to Opitz (5), stimulation of the hepatic nerve has relatively little effect on the flow through the portal vein which brings the main body of blood to the liver, and therefore such stimulation would certainly not be so effective as actual occlusion of that vessel in checking the blood flow. A failure of the blood pressure to rise markedly when both the hepatic artery and the portal vein are closed gives little support to the view that the rise is due to an obstruction in the hepatic stream. A second fact bearing on the question is that all the viscera may be removed from the abdominal cavity except the liver which is then supplied by the hepatic artery alone. On April 6, stimulation of the hepatic nerves under these circumstances caused a typical rise of blood pressure, from 126 to 148 mm. Hg. The maximal height was reached in 50 seconds and the pressure was still above the original level a minute and a half after the start of stimulation. It is hardly to be believed that a temporary narrowing of the hepatic artery could have this marked effect on the general blood pressure. A third consideration, indicating that there is a pressor substance given off from the liver, is the lasting effect of hepatic stimulation. If, after removal of the adrenal glands and severance of the hepatic nerves, the splanchnics are stimulated for 30 seconds, the blood pressure rises in consequence of vasoconstriction, but in a series of 11 such instances, the maximal level was reached in an average of 19 seconds, and the blood pressure had in all instances returned to normal within a minute and a quarter from the beginning of stimulation. If the rise of blood pressure, due to hepatic stimulation, were solely the consequence of vasoconstriction in the liver, similar results might be expected. Instead, as shown in figure 3, the maximal rise appears at the end of 45 seconds, i.e., after more than twice the time required for the maximal direct vascular effect; and, furthermore, the higher pressure persists for a relatively long period. We have in several instances taken re-

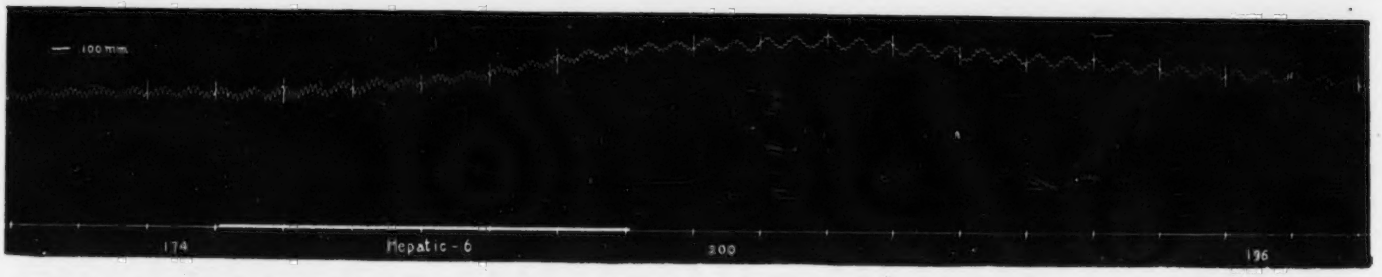

Fig. 3. Record showing effects on blood pressure and rate of the denervated heart of stimulating the hepatic nerves. The figures below the base line express heart rate per minute.

Fig. 4. Record showing sharp rise of blood pressure with acceleration of the pulse about 20 seconds after start of stimulation of hepatic nerves. The figures below the base line express heart rates per minute.

peated records until the pressure returned to the initial level. It is not unusual for two or three minutes to elapse before the former condition is restored. Neither the higher blood pressure nor the increased heart rate following hepatic stimulation can be regarded as due to concentration of adrenal secretion because of a lessened blood flow through the liver, for both effects are readily observable in animals from which the adrenals have previously been removed. Still another fact, which is illustrated in figure 4, is that occasionally the rise of blood pressure though beginning as usual a few seconds after the start of stimulation, shows a sharp rise after 20 seconds, i.e., at the same time that the heart begins to beat more rapidly. The coincidence of the rise of pressure and the increased rate may be interpreted as indicating that there is a simultaneous influence on both the blood vessels and the heart rate. It is improbable that the accelerated pulse in these instances accounts by itself for the higher level of pressure. Though the initial rise of pressure is probably due to constriction of the hepatic artery, we conclude, for the reasons stated above, that the continued rise and its persistence for a long period after stimulation has ceased is probably a consequence of the action of material given off from the liver when the hepatic nerves are excited.

Absence of the pupillary effect. The similarity of action of the hepatic agent and of adrenal secretion on both the heart rate and blood pressure might suggest that there would be a resemblance in other ways. In 1912, Joseph and Meltzer (6) called attention to the fact that, if the superior cervical ganglia had previously been removed, stimulation of the splanchnic nerves would cause dilatation of the pupil through a discharge from the adrenal glands. This reaction was confirmed by Elliott the same year (7). Stewart and Rogoff report that whereas splanchnic stimulation with the adrenal veins open causes a rise of blood pressure, a faster heart, and an expansion of the sensitized iris, the same stimulation after clipping of the adrenal veins, though inducing the other changes, has no effect on the iris (1). This result may be interpreted as showing that the material given off by the liver has no influence on the eye. We have tested the effects on the sensitized iris of hepatic stimulation itself. For example, on June 2, though such stimulation increased the heart rate 12 beats per minute and raised the blood pressure from 122 to 140 mm. Hg., it caused no pupillary change. Adrenal stimulation, however, had the typical effect. It appears, therefore, that the action of the hepatic agent does not resemble in all respects the action of adrenin.

The effect of asphyxia. We have repeatedly had occasion to observe that the efficiency of hepatic stimulation is markedly reduced or completely abolished if asphyxia is present or has recently occurred. For example, on January 7, the hepatic vessels (artery and portal vein) were closed for 75 seconds, during which the nerves were stimulated. There was no rise in the heart rate during the stimulation nor after the blood was allowed to flow again; and subsequent stimulations caused increases of only 6 and 8 beats, whereas previously stimulations of the same intensity had increased the rate 24, 18 and 18 beats respectively. Similar observations were made on January 20 and March 5. In these last two cases, the increments, which had been high (18, 32) before closure of the hepatic vessels, were reduced to 6 beats per minute immediately after, and only gradually returned to the former figures. In several instances of accidental failure of respiration and disappearance of the heart beat during operative procedures, the animals were resuscitated by a relatively large adrenalin injection and by artificial respiration. In none of these cases did hepatic stimulation induce a rise of heart rate. On February 19 the animal stopped breathing after some observations had been made and was recovered by artificial respiration alone. The increments which had been 12, 12 and 11 beats per minute before the asphyxia were 0, 2 and 6 when the hepatic nerves were stimulated at intervals after natural respiration was resumed. The action of the liver appears, therefore, to be highly sensitive to interruption of its normal blood and oxygen supply.

Relation of the hepatic agent to digestion. Inspection of table 1 shows that a wide variety of effects on the heart rate may be produced in different animals when the same nerve filaments are stimulated. The question arises as to why in some cases the rate is not accelerated by more than 4 or 6 beats per minute, whereas in other cases the increments range aboye 20 or 30 beats. This discrepancy was obvious from the first. As observations continued, it became clear that the variation was associated with the state of the animal at the time the experiment was being conducted. In table 1 the results listed in the first section were all from cases in which animals were fasting and in which the stomach and small intestine were empty. The results listed in the second section were obtained from animals which were digesting meat or meat and fat.[2] The explanation of this

[2] Three exceptional cases have not been included in table 1. In two of these hepatic stimulation caused marked accelerations (increases of 26 and 16 beats per minute on January 26, and increases of 18, 32, 10, 30, 26, 24 and 25 beats on

difference is deferred to a later paper. For the present we merely wish to point out that it can wholly account for the absence of reflex effects, or the very slight effects on the denervated heart after adrenalectomy, that were reported by Cannon in 1919 (3). In his experiments the animals were deprived of food for a day or two before the operation in order that the stomach might be empty and thus permit ready access to the adrenal glands. The difference between the results in fasting and in digesting animals explains also the large variation of effects on the denervated heart observed by Stewart and Rogoff when they stimulated the splanchnic nerves after removal of the adrenals.

SUMMARY

After removal of the adrenal glands, splanchnic stimulation will cause a faster beat of the denervated heart. Since this occurs when the inferior cava and the portal vein are closed below the liver, and since it does not occur when the hepatic nerves are cut, the inference is drawn that some agent arising in the liver is the occasion of the faster beat.

Stimulation of the hepatic nerves will cause an increased rate of the denervated heart, an effect appearing later than the similar adrenin effect and lasting for a longer time (see table 1 and figs. 1, 3 and 4).

Stimulation of the hepatic nerves will cause a rise of blood pressure (see figs. 2, 3 and 4). Evidence is adduced to show that this is not the consequence of a retarded blood flow through the liver: it does not occur on closure of the hepatic artery and vein; it occurs on hepatic stimulation though all abdominal viscera have been removed except the liver; and, unlike stimulation of splanchnic blood vessels alone, it long outlasts the period of stimulation.

Asphyxia is very promptly depressive in its influence on the effectiveness of hepatic stimulation.

The increments of heart rate vary widely. They are slight if the animal has been fasting, or is in poor condition; they are much greater

March 5), although the alimentary canal was nearly empty. These animals, however, were well nourished and in excellent physical condition. The third exception was noted in a well-fed cat, which was digesting meat, and in which hepatic stimulation three times repeated, called forth no increment of rate and thereafter evoked accelerations of only 6 and 8 beats per minute. This animal had been extraordinarily excitable, flying into a rage at the slightest provocation and showing much resistance when being etherized.

if the animal is digesting meat (see table 1). These differences can account for the discrepancies in Cannon's and Stewart and Rogoff's results after adrenalectomy.

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